(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 December 2004 (09.12.2004)

PCT

(10) International Publication Number
WO 2004/105762 A1

(51) International Patent Classification[7]: A61K 31/4995, A61P 33/06

(21) International Application Number: PCT/EP2004/005065

(22) International Filing Date: 12 May 2004 (12.05.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/EP03/05661 30 May 2003 (30.05.2003) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/105762 A1

(54) Title: MEDICAL USE OF DIAZABICYCLONONENE DERIVATIVES AS INHIBITORS OF PARASITE ASPARTIC PROTEASES

(57) Abstract: The invention relates to the use of 3,9-diazabicyclo[3.3.1]nonene derivatives and related compounds as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the pharmaceutical compositions containing one or more of those compounds and especially their use as inhibitors of plasmepsin II.

MEDICAL USE OF DIAZABICYCLONONENE DERIVATIVES AS INHIBITORS OF PARASITE ASPARTIC PROTEASES

In an earlier patent application, first published as WO 03/093267 A1 filed by the applicant (Actelion Pharmaceuticals Ltd), novel diazabicyclononene derivatives and their preparation as well as their use, especially as renin inhibitors, have been described. It has now been found that these compounds inhibit plasmepsin II. They are therefore useful as antimalarials.

The present invention is concerned with the use of diazabicyclononene derivatives against malaria pathogens and, in particular, relates to compounds of the general formula I. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula I and especially their use as plasmepsin II inhibitors for the treatment of malaria. Furthermore, these compounds can be regarded as inhibitors of other aspartyl proteases and might, therefore, be useful as inhibitors of plasmepsin I, plasmepsin IV or histo-aspartic protease (HAP) to treat malaria and as inhibitors of *Candida albicans* secreted aspartyl proteases to treat fungal infections.

Background of the invention:

Malaria is one of the most serious and complex health problems affecting humanity in the 21st century. The disease affects about 300 million people worldwide, killing 1 to 1.5 million people every year. Malaria is an infectious disease caused by four species of the protozoan parasite Plasmodium, P. falciparum being the most severe of the four. All attempts to develop vaccines against P. falciparum have failed so far. Therefore, therapies and preventive measures against malaria are confined to drugs. However, resistance to many of the currently available antimalarial drugs is spreading rapidly and new drugs are needed.

P. Falciparum enters the human body by way of bites of the female anopheles mosquito. The plasmodium parasite initially populates the liver, and during later

stages of the infectious cycle reproduces in red blood cells. During this stage, the parasite degrades hemoglobin and uses the degradation products as nutrients for growth [1]. Hemoglobin degradation is mediated by serine proteases and aspartic proteases. Aspartic proteases have been shown to be indispensable to parasite growth. A non-selective inhibitor of aspartic proteases, pepstatin, inhibits the growth of P. falciparum in red blood cells in vitro. The same results have been obtained with analogs of pepstatin [2], [3]. These results show that inhibition of parasite aspartic proteases interferes with the life cycle of P. falciparum. Consequently, aspartic proteases are targets for antimalarial drug development.

The present invention relates to the identification of low molecular weight, non-peptidic inhibitors of the plasmodium falciparum protease plasmepsin II or other related aspartic proteases to treat and/or prevent malaria.

Prior Art:

To date several classes of plasmepsin II inhibitors have been described in the literature. To the best of our knowledge, none of these compounds has entered clinical development so far. Research efforts within different structural classes of plasmepsin II inhibitors have recently been summarized and published [C. Boss et al.; *Curr. Med. Chem.* **2003**, *10*, 883-907 and references cited there]. Plasmepsin inhibitors based on a peptidomimetic or substrate-analogue approach are described in the following patents: US-05734054 (Pharmacopeia Inc), US-05892038 (Pharmacopeia Inc.), WO-00114331 (University of California, Berkley), WO-02074719 (Johns Hopkins University), and publications: D. Nöteberg, E. Hamelink, J. Hulten, M. Wahlgren, L. Vrang, B. Samuelsson, A. Hallberg, *J. Med. Chem.*, **2003**, *46*, 734-746. K. Oscarsson, S. Oscarson, L. Vrang, E. Hamelink, A. Hallberg, B. Samuelsson, *Bioorg. Med. Chem.*, **2003**, *11*, 1235-1246. A. Dahlgren, I. Kvarnström, L. Vrang, E. Hamelink, A. Hallberg, A. Rosenquist, B. Samuelsson, *Bioorg. Med. Chem.*, **2003**, *11*, 827-841. Non-peptidomimetic plasmepsin II inhibitors are described in the following publications: WO-00224649 (Actelion Pharmaceuticals Ltd.), WO-00238543 (Actelion Pharmaceuticals Ltd.) and WO-09912532 (F. Hoffmann-La Roche

Ltd.). Only one publication was found so far that describes non-peptidomimetic, rationally designed plasmepsin II inhibitors: Carcache, D. A.; Hörtner, S. R.; Bertogg A.; Binkert, C.; Bur, D.; Märki, H.-P.; Dorn, A.; Diederich, F.; *ChemBioChem*, **2002**, *11*, 1137.

The compounds of general formula I were tested against plasmepsin II, HIV-protease, human cathepsin D, human cathepsin E and human renin in order to determine their biological activity and their selectivity profile.

In vitro Assays:

The fluorescence resonance energy transfer (FRET) assay for HIV, plasmepsin II, human cathepsin D and human cathepsin E.

The assay conditions were selected according to reports in the literature [4 - 7]. The FRET assay was performed in white polysorp plates (Fluoronunc, cat n° 437842 A). The assay buffer consisted of 50 mM sodium acetate pH 5, 12,5% glycerol, 0.1% BSA + 392 mM NaCl (for HIV-protease).
The incubates per well were composed of:

- 160 µl buffer
- 10 µl inhibitor (in DMSO)
- 10 µl of the corresponding substrate in DMSO (see table A) to a final concentration of 1 µM
- 20 µl of enzyme to a final amount of x ng per assay tube (x = 10 ng/assay tube plasmepsin II, x = 100 ng/assay tube HIV-protease, x = 10 ng/assay tube human cathepsin E and x = 20 ng/assay tube human cathepsin D)

The reactions were initiated by addition of the enzyme. The assay was incubated at 37°C for 30 min (for human cathepsin E), 40 min (for plasmepsin II and HIV-protease) or 120 min (for human cathepsin D). The reactions were stopped by adding 10% (v/v) of a 1 M solution of Tris-base. Product-accumulation was monitored by measuring the fluorescence at 460 nm.

Auto-fluorescence of all the test substances is determined in assay buffer in the absence of substrate and enzyme and this value was

Aspartyl protease	**substrate**		**enzyme concentration** ng/at (nM)	**Buffer**	**pH**	**incubation time** minutes
	sequence	substrate concentration µM				
HIV	Dabcyl-Abu-SQNY:PIVN-EDANS	1	100 (22.5)	50 mM Na acetate ; 12,5 % glycerol ; 0.1 % BSA 392 mM NaCl	5	40
Plasmepsin II	Dabcyl-ERNleF:LSFP-EDANS	1	10 (1.25)	50 mM Na acetate ; 12,5 % glycerol ; 0.1% BSA	5	40
h Cathepsin D	Dabcyl-ERNleF:LSFP-EDANS	1	20 (2.5)	50 mM Na acetate ; 12,5 % glycerol ; 0.1% BSA	5	120
h Cathepsin E	Dabcyl-ERNleF:LSFP-EDANS	1	10 (1.25)	50 mM Na acetate ; 12,5 % glycerol ; 0.1% BSA	5	30

subtracted from the final signal.

5

Table A: Summary of the conditions used for the aspartyl proteases fluorescent assays. (at = assay tube)

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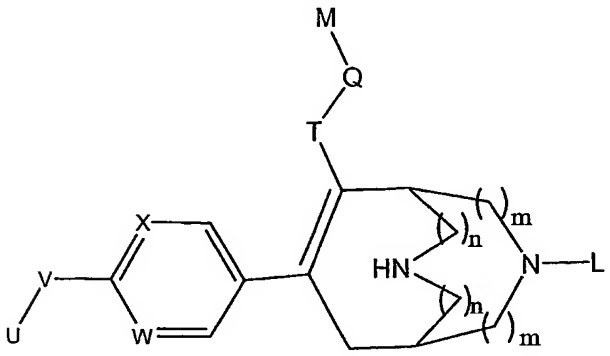
In particular, the present invention relates to pharmaceutical compositions for treating diseases demanding the inhibition of parasitic aspartic proteases containing one or more compounds of the general formula I,



Formula I

wherein

X and W represent a nitrogen atom or a -CH- group and may be the same or different;

V represents $-(CH_2)_r-$; $-A-(CH_2)_s-$; $-CH_2-A-(CH_2)_t-$; $-(CH_2)_s-A-$; $-(CH_2)_2-A-(CH_2)_u-$; $-A-(CH_2)_v-B-$; $-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-B-$; $-CH_2-CH_2-CH_2-A-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-CH_2-$; $-CH_2-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-CH_2-B-$; or $-CH_2-CH_2-A-CH_2-CH_2-B-$;

A and B independently represent -O-; -S-; -SO-; $-SO_2-$;

U represents aryl; heteroaryl;

T represents $-CONR^1-$; $-(CH_2)_pOCO-$; $-(CH_2)_pN(R^1)CO-$; $-(CH_2)_pN(R^1)SO_2-$; or -COO-;

Q represents lower alkylene; lower alkenylene;

M represents hydrogen; cycloalkyl; aryl; heterocyclyl; heteroaryl;

L represents -R^3; -COR^3; -$COOR^3$; -$CONR^2R^3$; -SO_2R^3; -$SO_2NR^2R^3$; -$COCH(Aryl)_2$;

R^1 represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

R^2 and $R^{2'}$ independently represent hydrogen; lower alkyl; lower alkenyl; cycloalkyl; cycloalkyl - lower alkyl;

R^3 represents hydrogen; lower alkyl; lower alkenyl; cycloalkyl; aryl; heteroaryl; heterocyclyl; cycloalkyl - lower alkyl; aryl - lower alkyl; heteroaryl - lower alkyl; heterocyclyl - lower alkyl; aryloxy - lower alkyl; heteroaryloxy - lower alkyl, whereby these groups may be unsubstituted or mono-, di- or trisubstituted with hydroxy, -$OCOR^2$, -$COOR^2$, lower alkoxy, cyano, -$CONR^2R^{2'}$, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), -$NH(NH)NH_2$, -$NR^4R^{4'}$ or lower alkyl, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

R^4 and $R^{4'}$ independently represents hydrogen; lower alkyl; cycloalkyl; cycloalkyl - lower alkyl; hydroxy - lower alkyl; -$COOR^2$; -$CONH_2$;

m and n represent the integer 0 or 1, with the proviso that in case m represents the integer 1 n is the integer 0, and in case n represents the integer 1 m is the integer 0;

p is the integer 1, 2, 3 or 4;
r is the integer 3, 4, 5, or 6;
s is the integer 2, 3, 4, or 5;
t is the integer 1, 2, 3, or 4;
u is the integer 1, 2, or 3;

v is the integer 2, 3, or 4;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms and suitable carrier material.

In the definitions of general formula **I** – if not otherwise stated – the term **lower alkyl**, alone or in combination with other groups, means saturated, straight and branched chain groups with one to seven carbon atoms, preferably one to four carbon atoms that can be optionally substituted by halogens. Examples of lower alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and heptyl. The methyl, ethyl and isopropyl groups are preferred.

The term **lower alkoxy** refers to a R-O group, wherein R is a lower alkyl. Examples of lower alkoxy groups are methoxy, ethoxy, propoxy, iso-propoxy, iso-butoxy, sec-butoxy and tert-butoxy.

The term **lower alkenyl**, alone or in combination with other groups, means straight and branched chain groups comprising an olefinic bond and two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkenyl are vinyl, propenyl or butenyl.

The term **lower alkinyl**, alone or in combination with other groups, means straight and branched chain groups comprising a triple bond and two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkinyl are ethinyl, propinyl or butinyl.

The term **lower alkylene**, alone or in combination with other groups, means straight and branched divalent chain groups with one to seven carbon atoms,

preferably one to four carbon atoms that can be optionally substituted by halogens. Examples of lower alkylene are ethylene, propylene or butylene.

The term **lower alkenylene**, alone or in combination with other groups, means straight and branched divalent chain groups comprising an olefinic bond and two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkenylene are vinylene, propenylene and butenylene.

The term **lower alkylenedioxy**, refers to a lower alkylene substituted at each end by an oxygen atom. Examples of lower alkylenedioxy groups are preferably methylenedioxy and ethylenedioxy.

The term **lower alkylenoxy** refers to a lower alkylene substituted at one end by an oxygen atom. Examples of lower alkylenoxy groups are preferably ethylenoxy and propylenoxy.

The term **halogen** means fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine and bromine.

The term **cycloalkyl** alone or in combination, means a saturated cyclic hydrocarbon ring system with 3 to 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, which can be optionally mono- or multisubstituted by lower alkyl, lower alkenyl, lower alkenylene, lower alkoxy, lower alkylenoxy, lower alkylenedioxy, hydroxy, halogen, $-CF_3$, $-NR^1R^{1'}$, $-NR^1C(O)R^{1'}$, $-NR^1S(O_2)R1'$, $-C(O)NR^1R^{1'}$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^{1'}$, whereby $R^{1'}$ represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl. The cyclopropyl group is a preferred group.

The term **aryl**, alone or in combination, relates to the phenyl, the naphthyl or the indanyl group, preferably the phenyl group, which can be optionally mono- or multisubstituted by lower alkyl, lower alkenyl, lower alkinyl, lower alkenylene or lower alkylene forming with the aryl ring a five- or six-membered ring, lower alkoxy, lower alkylenedioxy, lower alkylenoxy, hydroxy, hydroxy-lower alkyl, halogen, cyano, $-CF_3$, $-OCF_3$, $-NR^1R^{1'}$, $-NR^1R^{1'}$ - lower alkyl, $-NR^1C(O)R^{1'}$, $-NR^1S(O_2)R^1$, $-C(O)NR^1R^{1'}$, $-NO_2$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^{1'}$, benzyloxy, whereby $R^{1'}$ represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl. The cyclopropyl group is a preferred group. Preferred substituents are halogen, lower alkoxy, lower alkyl.

The term **aryloxy** refers to an Ar-O group, wherein Ar is an aryl. An example of lower aryloxy groups is phenoxy.

The term **heterocyclyl**, alone or in combination, means saturated or unsaturated (but not aromatic) five-, six- or seven-membered rings containing one or two nitrogen, oxygen or sulfur atoms which may be the same or different and which rings can be optionally substituted with lower alkyl, hydroxy, lower alkoxy and halogen. The nitrogen atoms if present, can be substituted by a $-COOR^2$ group. Examples of such rings are piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, 1,4-dioxanyl, pyrrolidinyl, tetrahydrofuranyl, dihydropyrrolyl, imidazolidinyl, dihydropyrazolyl, pyrazolidinyl, dihydroquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl.

The term **heteroaryl**, alone or in combination, means six-membered aromatic rings containing one to four nitrogen atoms; benzofused six-membered aromatic rings containing one to three nitrogen atoms; five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; benzofused five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; five-membered aromatic rings containing one oxygen and one nitrogen atom and benzofused derivatives thereof; five-membered aromatic rings containing a sulfur

and a nitrogen or an oxygen atom and benzofused derivatives thereof; five-membered aromatic rings containing two nitrogen atoms and benzofused derivatives thereof; five-membered aromatic rings containing three nitrogen atoms and benzofused derivatives thereof, or a tetrazolyl ring. Examples of such ring systems are furanyl, thiophenyl, pyrrolyl, pyridinyl, pyrimidinyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, triazinyl, thiazinyl, thiazolyl, isothiazolyl, pyridazinyl, pyrazolyl, oxazolyl, isoxazolyl, coumarinyl, benzothiophenyl, quinazolinyl, quinoxalinyl. Such rings may be adequatly substituted with lower alkyl, lower alkenyl, lower alkinyl, lower alkylene, lowrr alkenylene, lower alkylenedioxy, lower alkyleneoxy, hydroxy-lower alkyl, lower alkoxy, hydroxy, halogen, cyano, $-CF_3$, $-OCF_3$, $-NR^1R^{1'}$, $-NR^1R^{1'}$ - lower alkyl, $-N(R^1)COR^1$, $-N(R^1)SO_2R^1$, $-CONR^1R^{1'}$, $-NO_2$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^{1'}$, another aryl, another heteroaryl or another heterocyclyl and the like, whereby $R^{1'}$ represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl. The cyclopropyl group is a preferred group.

The term **heteroaryloxy** refers to a Het-O group, wherein Het is a heteroaryl.

The term **sp3-hybridized** refers to a carbom atom and means that this carbon atom forms four bonds to four substituents placed in a tetragonal fashion around this carbon atom.

The expression **pharmaceutically acceptable** salts encompasses either salts with inorganic acids or organic acids like hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic acid, and the like that are non toxic to living organisms or in case the compound of formula **I** is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide and the like.

The compounds of the general formula I can contain two or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form and pharmaceutically acceptable salts therof.
The present invention encompasses all these forms. Mixtures may be separated in a manner known *per se*, i.e. by column chromatography, thin layer chromatography, HPLC or crystallization.

Especially preferred compounds of the invention are listed in table 1 (page 154).

The compounds of general formula I and their pharmaceutically acceptable salts may be used as therapeutics e.g. in form of pharmaceutical compositions. The pharmaceutical compositions may particularly be used for treatment of disorders associated with the role of plasmepsin II and which require the inhibition of plasmepsin II for treatment. They may especially be used for treatment and/or prevention of malaria or diseases caused by protozoal infection. These pharmaceutical compositions may also contain aside of one or more compounds of the general formula I a known plasmepsin II inhibitor, a known antimalarial or known HIV protease inhibitor.

Further, these pharmaceutical compositions may also be used for treatment or prevention of diseases demanding the inhibition of parasitic aspartic proteases, particularly for malaria or protozoal infections.

The invention also relates to the use of pharmaceutical compositions as defined above for treatment or prevention of diseases demanding the inhibition of parasitic aspartic proteases in combination with a known plasmepsin II inhibitor, a known antimalarial or a known HIV protease inhibitor or another known anti-HIV treatment.

In addition, compounds of formula I are useful for the preparation of a medicament for the treatment or prevention of diseases demanding the inhibition of parasitic aspartic proteases, particularly malaria or protozoal infection. These compounds are more particularly useful for diseases demanding the inhibition of parasitic aspartic proteases in combination with a known plasmepsin II inhibitor, a known antimalarial or a known HIV protease inhibitor or another known anti-HIV treatment.

Another aspect of the invention concerns a method of treating a patient suffering from a disease requiring the inhibition of parasitic aspartic proteases by administering a pharmaceutical composition comprising a compound of the general formula I. Regarding the administration, the dosage of compounds of formula I can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage between 1 mg and 1000 mg, between 50 mg and 500 mg, comes into consideration.

The pharmaceutical preparations conveniently contain between 1 mg and 500 mg, preferably between 5 mg and 200 mg of a compound of formula I.

A further aspect of the invention concerns a process for the preparation of the above-mentioned pharmaceutical composition by mixing one or more active ingredients of formula I with inert excipients in a manner known per se.

The compounds of formula I may also be used in combination with one or more other therapeutically useful substances.

All forms of prodrugs leading to an active component comprised in general formula I are included in the present invention.

The compounds of general formula I can be manufactured by the methods given below, in accordance with procedures given in WO 03/093267 A1 (Actelion Pharmaceuticals Ltd) or by analogous methods.

The compounds of formula I and their pharmaceutically acceptable acid addition salts can be used as medicaments, e. g. in the form of pharmaceutical preparations for enteral, parenteral, or topical administration. They can be administered, for example, perorally, e. g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e. g. in the form of suppositories, parenterally, e. g. in the form of injection solutions or infusion solutions, or topically, e. g. in the form of ointments, creams or oils.

The production of pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and their pharmaceutically acceptable acid addition salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants in a manner known per se.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers are, however, required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injections are, for example, water, alcohols, polyols, glycerols and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical

preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

General remarks

The compounds were characterized at least by LC-MS and ^{1}H-NMR. Only the LC-MS data are given in the earlier application filed by the applicant (Actelion Pharmaceuticals Ltd.).

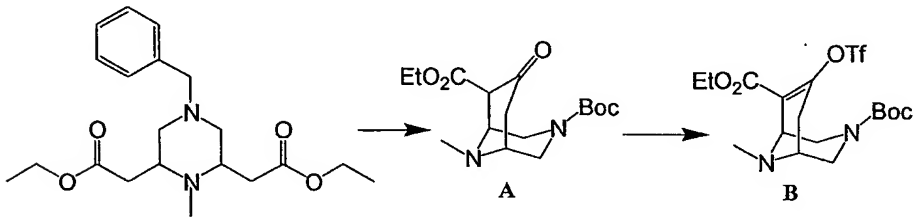
Synthetic Approaches for the preparation of compounds of general formula I:

Preparation of the precursors:

Precursors are compounds which were prepared as key intermediates and/or building blocks and which were suitable for further transformations in parallel chemistry.

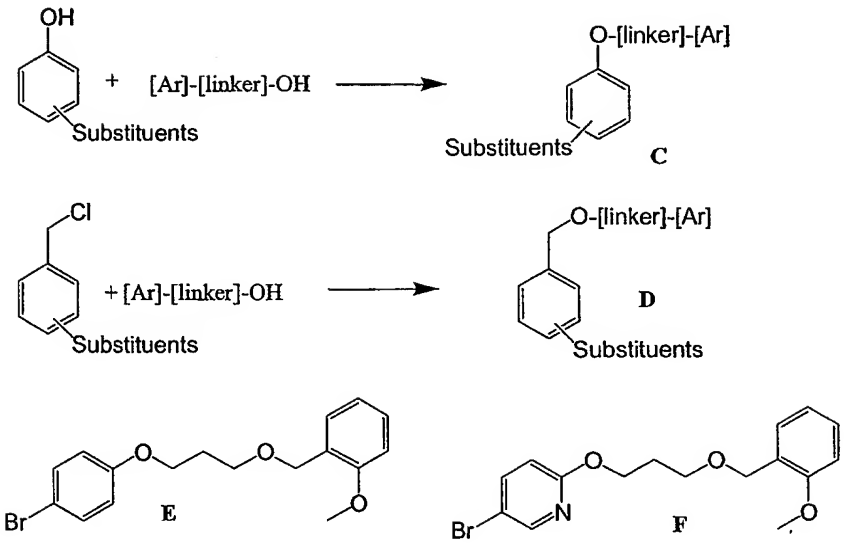
Bicyclononanone **A** was prepared from (4-benzyl-6-ethoxycarbonylmethyl-1-methylpiperazin-2-yl) acetic acid ethyl ester (Patent Application WO92/05174) as described in Scheme 1. Derivative **A** might also be present as enol form. In order to allow a coupling at the 7-position of bicyclononane **A** with aryl bromides, the vinyl triflate derivative **B** was prepared.

Scheme 1



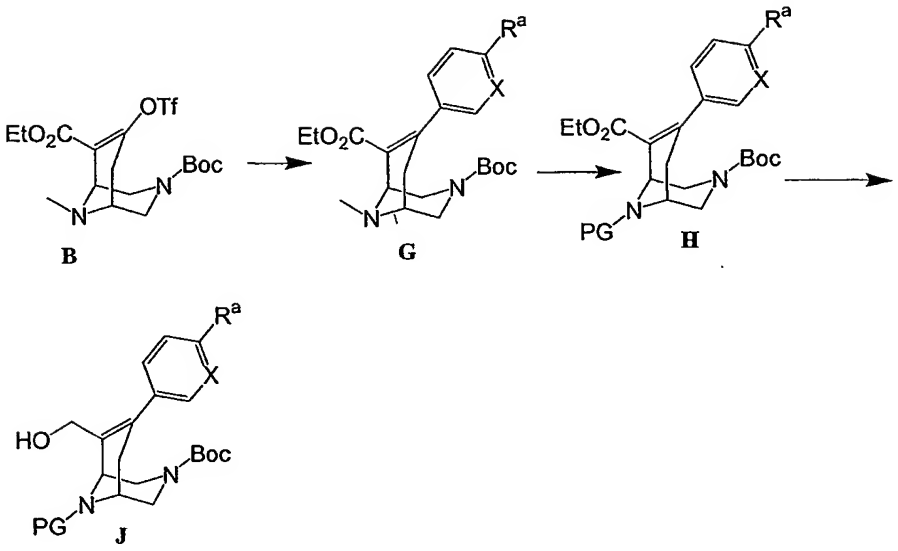
The bromoaryl components can be prepared as described in Scheme 2. A *Mitsunobu* coupling (→ compounds of type **C**) or the alkylation of an alcohol with a benzylic chloride (or bromide, → compounds of type **D**) are often the most convenient methods. Derivatives **E** and **F** were prepared in one step from 1-(3-chloropropoxymethyl)-2-methoxybenzene (Vieira E. *et al.*, *Bioorg. Med. Chem. Letters*, **1999**, *9*, 1397) or 3-(5-bromopyridin-2-yloxy)propan-1-ol (Patent Application WO 98/39328) according to these methods. Other methods for the preparation of ethers or thioethers, like a *Williamson* synthesis, might be used as well (see e.g. March, J, "Advanced Organic Chemistry,", 3rd ed., John Wiley and sons, 1985).

Scheme 2



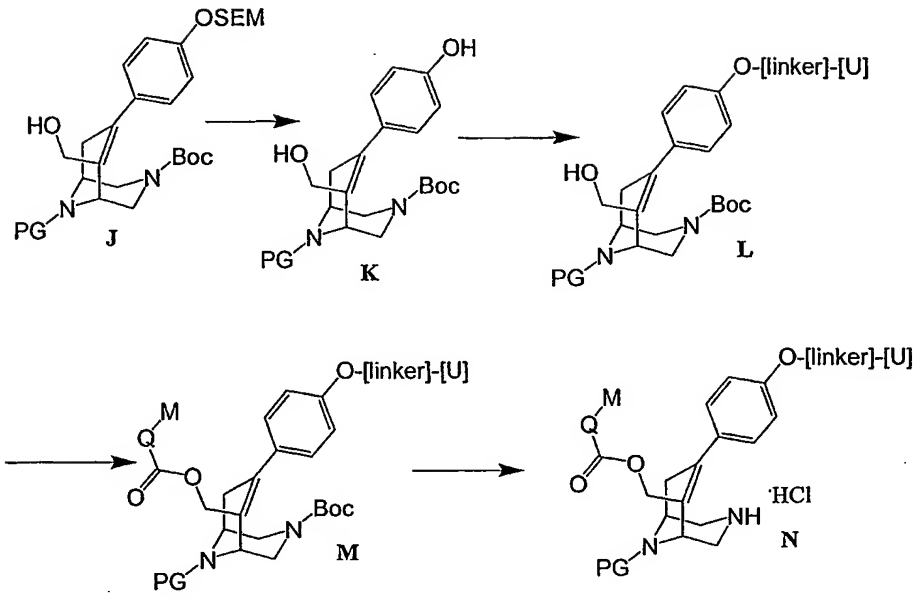
As shown in Scheme 3, these bromoaryl derivatives might then be coupled to triflate **B** in the presence of $Pd(PPh_3)_4$ or a related Pd(0)-complex in order to obtain bicyclononenes **G** (for details see the corresponding examples). Protective group manipulation would lead to the bicyclononenes **H**, which can finally be reduced to the alcohol derivatives **J**.

Scheme 3



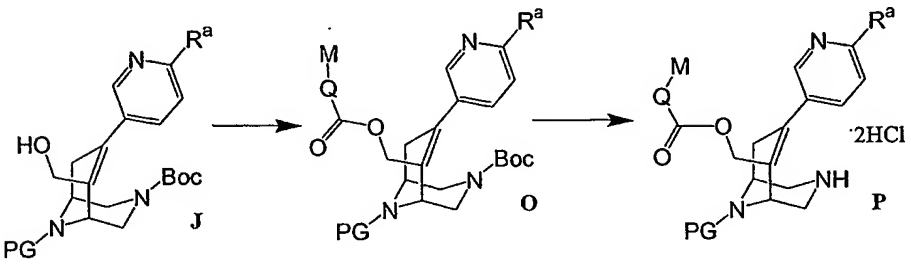
If R^a is O-SEM and X is CH, in compounds of type **J**, the SEM-protecting group can be cleaved under slightly acidic conditions, while the Boc-protecting group remains untouched as illustrated in Scheme 4. The phenolic moiety of bicyclononene **K** might then be alkylated to bicyclononene **L**. This alkohol intermediate would be transformed into the ester **M**, and the Boc-protecting group can finally be cleaved to yield precursor **N**.

Scheme 4



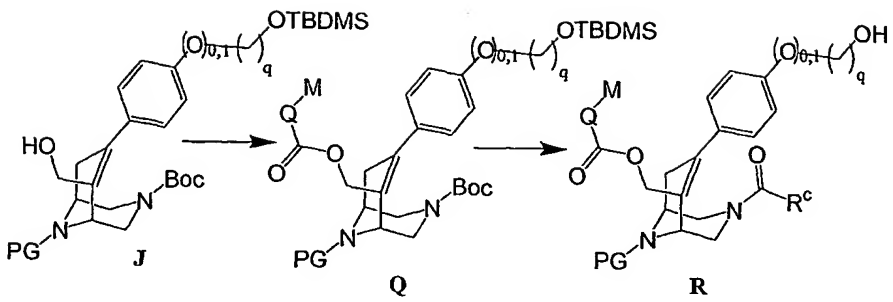
If X is N (Scheme 3), bicyclononenes of type **J** can be esterified to bicyclononenes **O** that can be deprotected to precursors **P** (Scheme 5).

Scheme 5



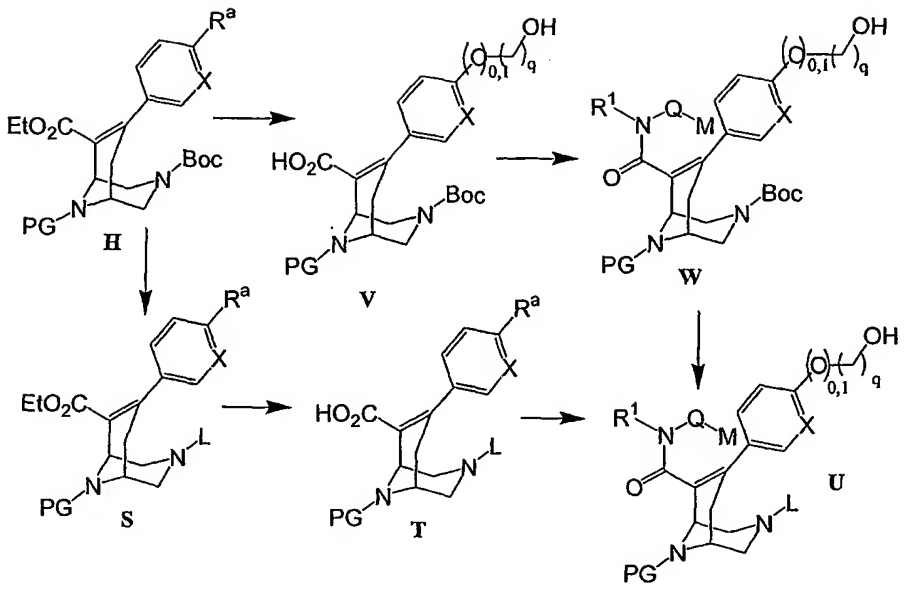
If, in alkohols **J**, X is CH (Scheme 6) and, for instance, R^a is $O(CH_2)_qOTBDMS$ or $(CH_2)_qOTBDMS$ (Scheme 3), an esterification might lead to bicyclononenes **Q** (Scheme 6). Under acidic conditions, both the Boc- and the TBDMS-groups would be cleaved and the secondary amine might be acylated, sulfonated, or alkylated to yield precursors **R**.

Scheme 6



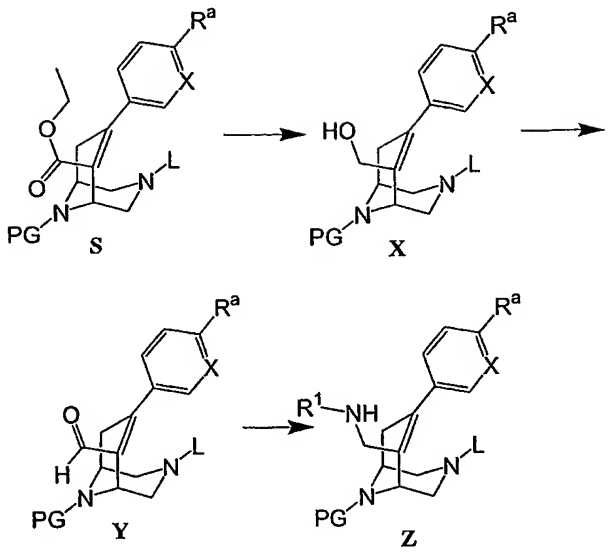
As illustrated in Scheme 7, the Boc-protecting group of bicyclononenes **H** might be cleaved and the resulting secondary amine acylated, sulfonated, or *N*-alkylated to bicyclononenes **S**. Saponification of the ester would lead to precursors **T**. If, for instance, R^a is $O(CH_2)_nOTBDMS$ or $(CH_2)_nOTBDMS$, the silyl ether might be cleaved simultaneously during the cleavage of the Boc-protecting group or during the saponification. The acid might be transformed into an amide to lead to precursors **U**. Alternatively, amides **U** can be prepared from bicyclononenes **H** through the acids **V**, with simultaneous cleavage of the silyl ether. Reaction of the acids **V** with amines might give the amides **W** that can be transformed into precursors **U**. The amines can be prepared according to the literature or as described in the experimental part.

Scheme 7



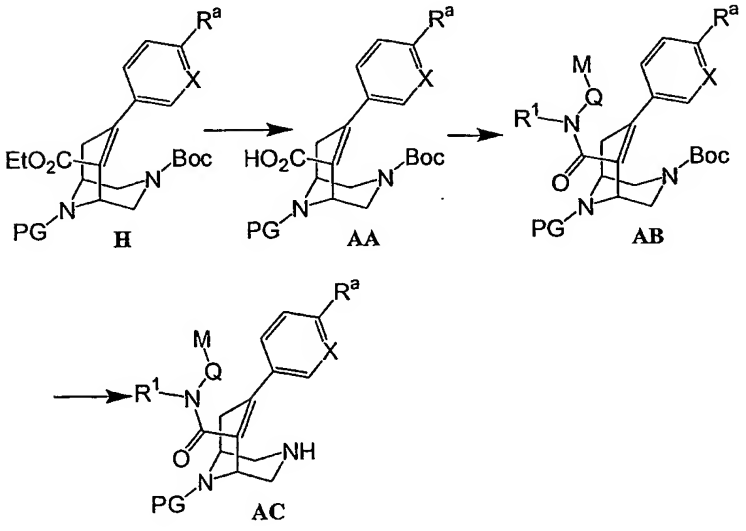
As illustrated in Scheme 8, the bicyclononenes **S** might be reduced to the corresponding alcohols **X**. The alcohol derivative **X** might then be oxidised to the aldehydes **Y**, which might transformed to the precursors **Z** by reductive amination.

Scheme 8



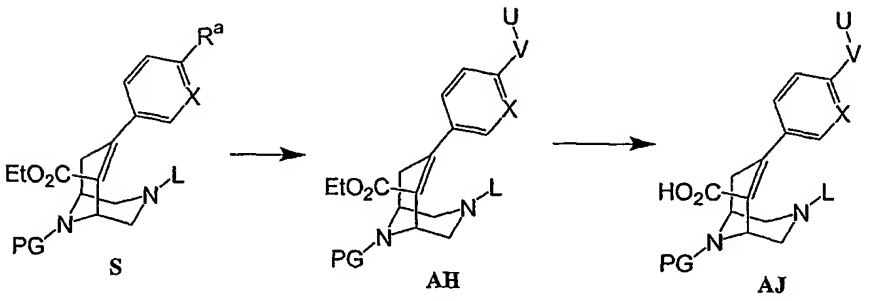
As shown in Scheme 9, a compound of type **H** might also be saponified to a compound of type **AA**. After amide coupling to a derivative of type **AB**, removal of the Boc-group would yield a precursor of type **AC**.

Scheme 9



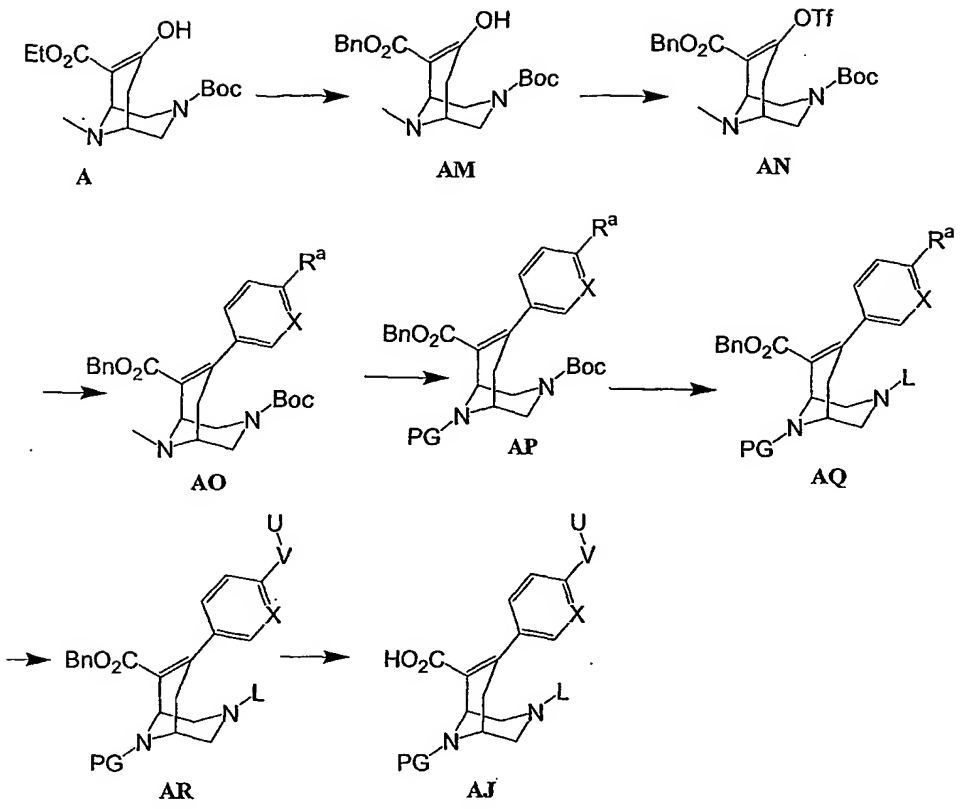
As illustrated in Scheme 10, a compound of type **S** might also be transformed into a compound of type **AH** that in turn can be saponified to a precursor of type **AJ**.

Scheme 10



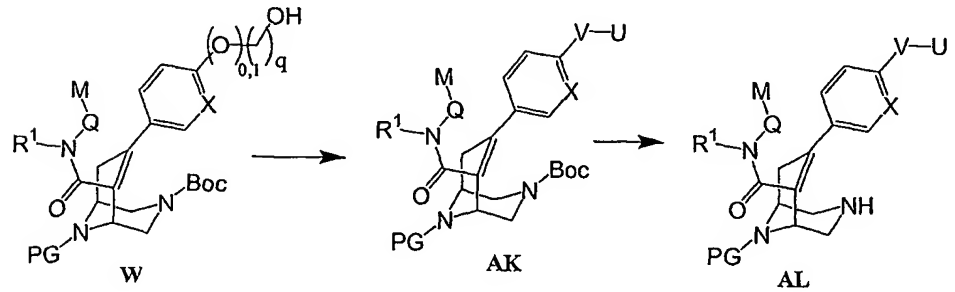
Alternatively precursors of type **AJ** might be prepared from bicyclononanone **A**, but using the benzyl ester instead of the ethyl ester, as illustrated in Scheme 11. After a transesterification to compound **AM** similar reactions as described here above would lead to compounds **AN**, **AO**, **AP**, **AQ** ,**AR** and finally **AJ**.

Scheme 11



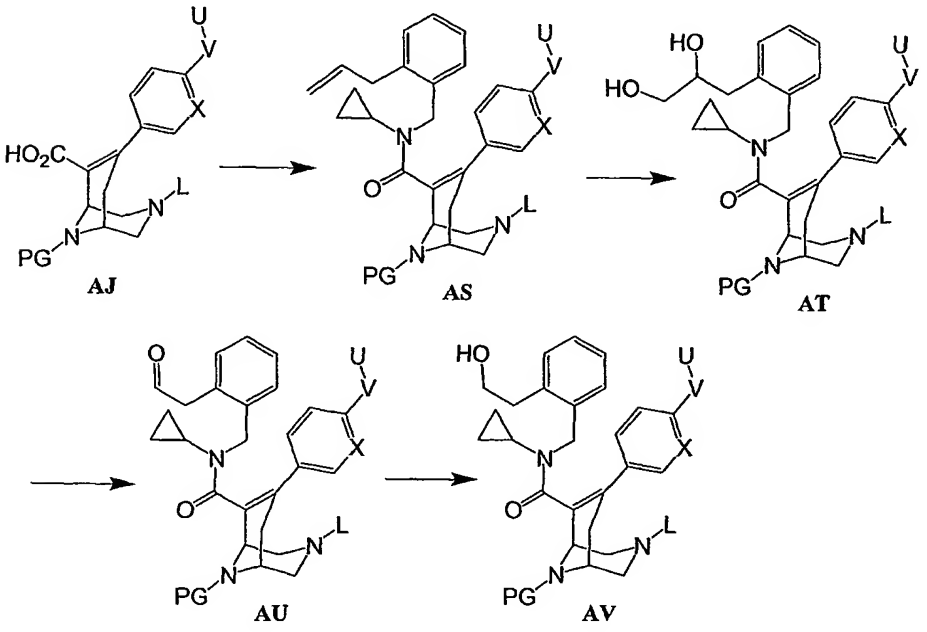
As shown in Scheme 12 a precursor of type **AL** might be prepared as well in two steps from a compound of type **W**.

Scheme 12



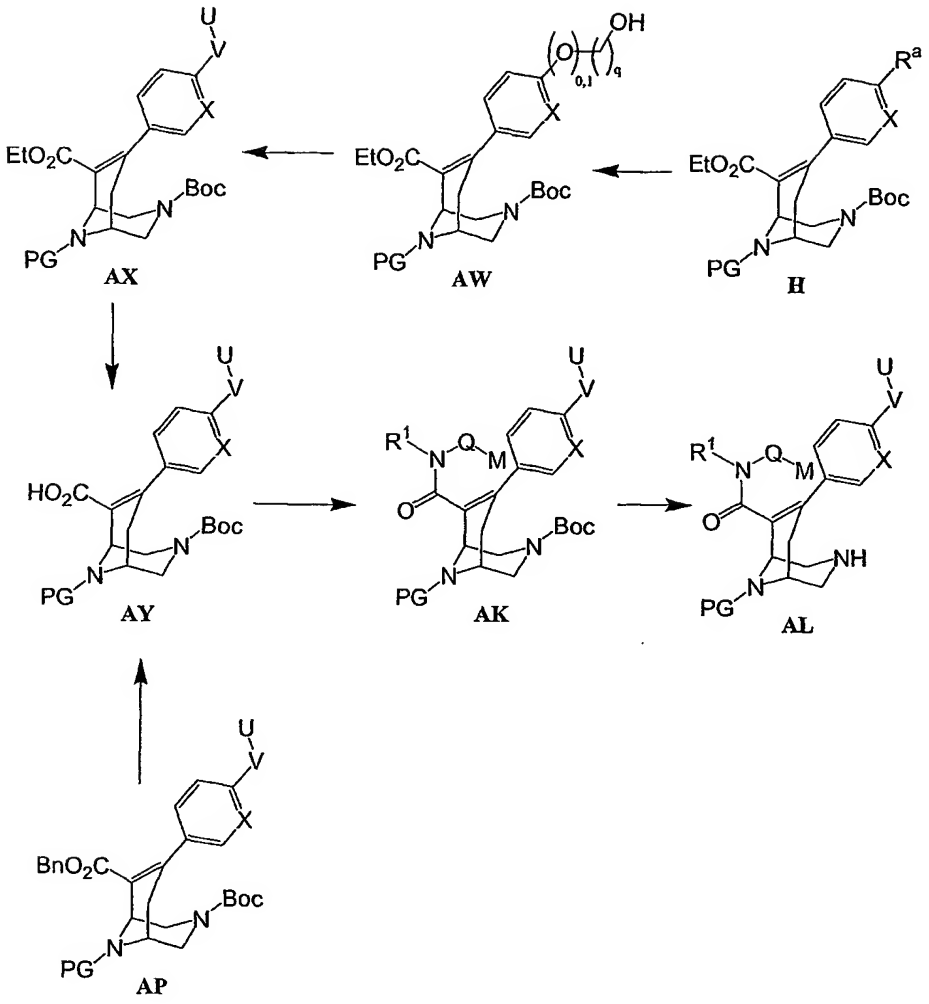
Sometimes it might be necessary to transform a substituent further after attaching it on the bicyclic template. For instance a compound of type **AS**, obtained by amide coupling from a compound of type **AJ**, might be transformed into a precursor of type **AT**, **AU**, or **AV**, as illustrated in Scheme 13.

Scheme 13



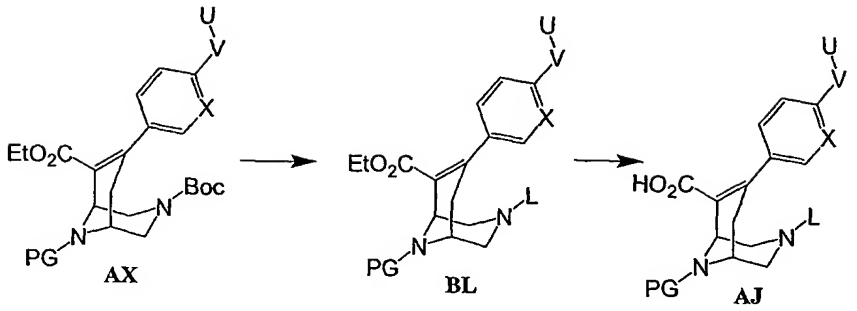
As illustrated in Scheme 14 compounds of type **H** might be deprotected into compounds of type **AW**. This type of compounds might be then transformed into compounds of type **AX** and finally into compounds of type **AY**. Compounds of type **AY** might also be prepared from compounds of type **AP**. Compounds of type **AY** might be transformed into compounds of type **AK**. Compounds of type **AK** might be finally transformed into precursors of type **AL**.

Scheme 14



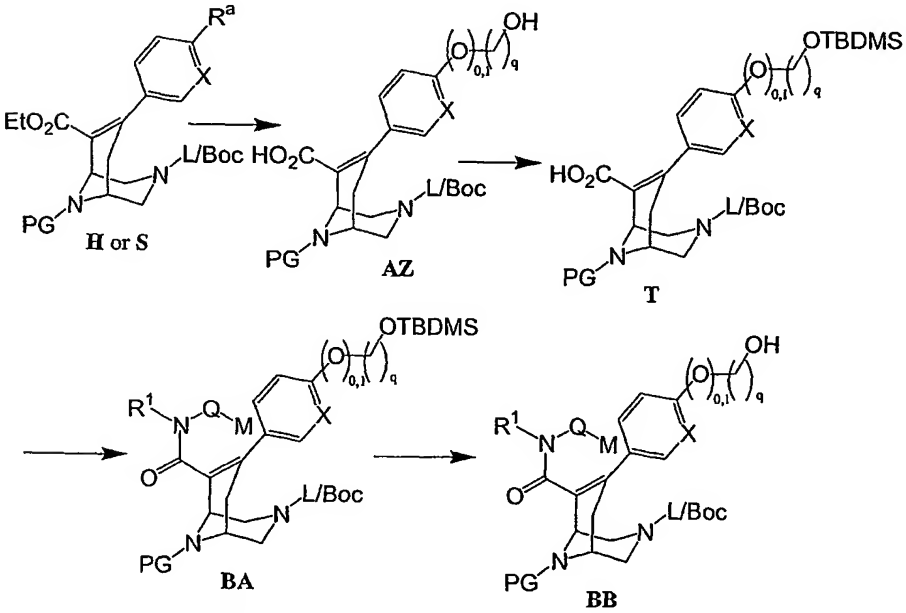
5 Alternatively, as shown in Scheme 15, **AX** might be transformed into a compound of type **BL**, than might be then lead to a compound of type **AJ**.

Scheme 15



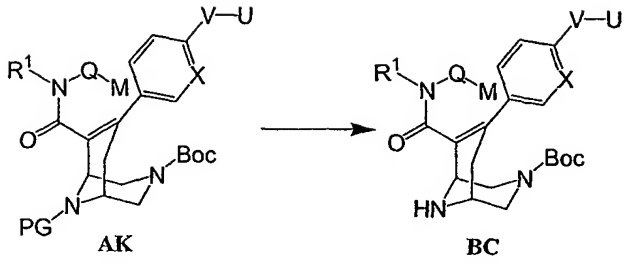
As shown in Scheme 16 compounds of type **H** or **S** might be transformed into compounds of type **AZ** (the substituent at the N(3) position be L or Boc). Then compounds of type **T** might be obtained that might be then transformed into compounds of type **BA**. Finally precursors of type **BB** might be prepared.

Scheme 16



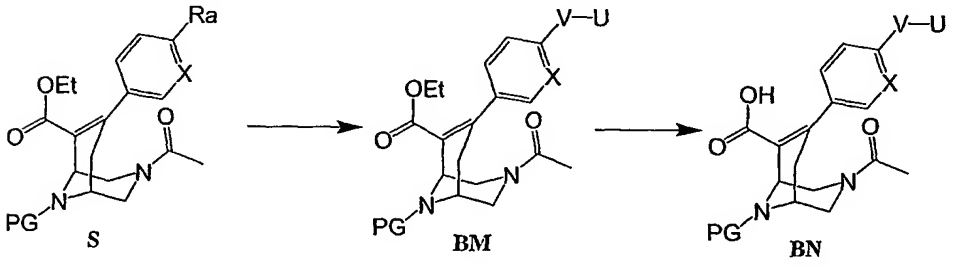
Also, as shown in Scheme 17, compounds of type **AK** might be transformed into precursors of type **BC**.

Scheme 17



Also, a compound of type **S** might be transformed into a compound of type **BM**, as shown in Scheme 18. A compound of type BM might be then saponified into a precursor of type **BN**.

Scheme 18



Preparation of the secondary amines

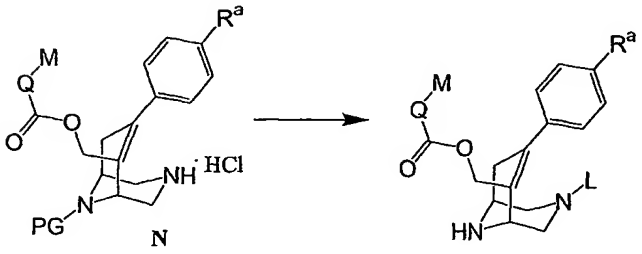
It might be necessary to prepare secondary amines as well. This might be done by reductive amination from the corresponding amine and aldehyde, or by amide coupling, from the corresponding amine and carboxylic acid, followed by reduction with LAH or borane. These standard procedures are well-described in the literature. (2-Allylphenyl)cyclopropylamine, necessary for instance in Scheme 13, might be prepared by allylation of 2-bromobenzaldehyde, protected as an acetal; subsequent deprotection to the 2-allylbenzaldehyde and reductive amination would lead to the desired amine.

Preparation of final compounds

From precursors prepared as described above, the final compounds can be prepared using parallel chemistry techniques. For the specific examples, see the experimental part.

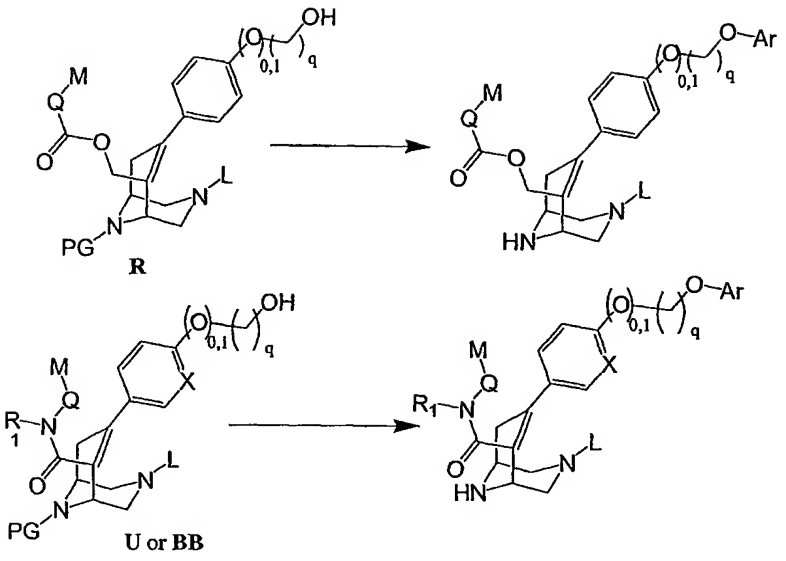
Diazabicyclononenes of type of **N** can be acylated, or alkylated, or sulfonated, using standard procedures (Scheme 19), and then directly deprotected to yield the final compounds (for numbering, see specific examples). In each case, purification by preparative HPLC might give the corresponding TFA salts or formate salts.

Scheme 19



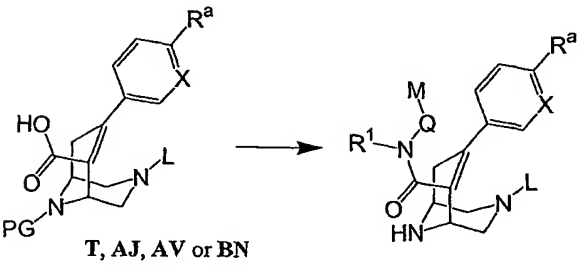
Precursors **R**, **U** or **BB** (with a L-substituent at the N(3)-position) might be transformed into the corresponding aryl ethers (Scheme 20), using the *Mitsunobu* reaction conditions. After deprotection, the final compounds are obtained.

Scheme 20



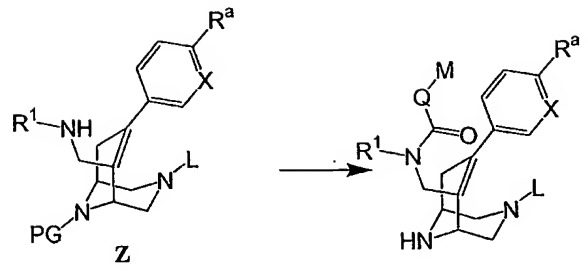
Precursors **T**, **AJ** or **AV** might be submitted to an amide coupling (Scheme 21). Deprotection would lead to the desired final compounds.

Scheme 21



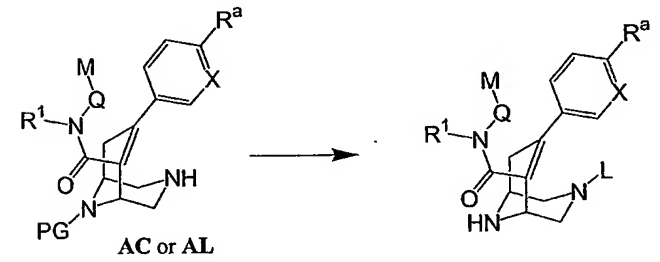
Compounds **Z** might be reacted with acylating (or sulfonating) reagents to lead to the corresponding amides (or sulfonamides) as well (Scheme 22). Deprotection would lead to the final compounds.

Scheme 22



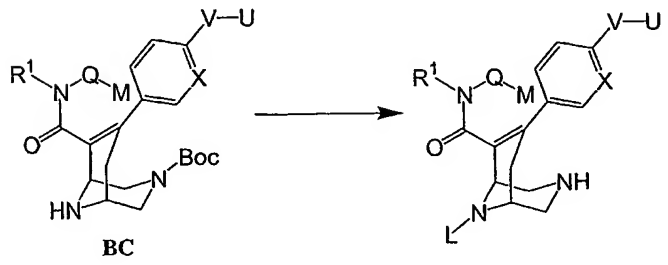
Compounds of type **AC** or **AL** can be reacted as well with acylating, sulfonating or alkylating reagents (Scheme 23). After deprotection, the final compounds would be obtained.

Scheme 23



Precursors of type **BC** might also lead to final compounds as indicated in Scheme 24.

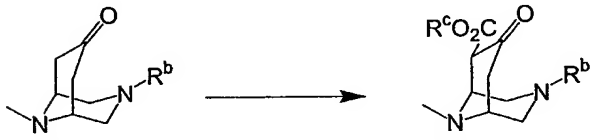
Scheme 24



Enantioselective synthesis:

The compounds of the present invention contain at least two chiral centers which, however, are not independent from each other. The synthetic methods presented so far might lead to racemates. Both enantiomers might be prepared selectively starting from a *meso*-bicyclononane derivative, like compound **AD** (Blount B. K., Robinson, R., *J. Chem. Soc.*, **1932**, 2485) or **AE**, prepared similarly to compound **A** with a subsequent decarboxylation (Scheme 25). For instance, compound **AE** might be stereoselectively acylated to bicyclononane derivatives **AF** or **AG** as already described elsewhere for similar compounds (Majewski M., Lasny R., *J. Org. Chem.*, **1995**, *60*, 5825). Similarly, the other enantiomer might be prepared.

Scheme 25

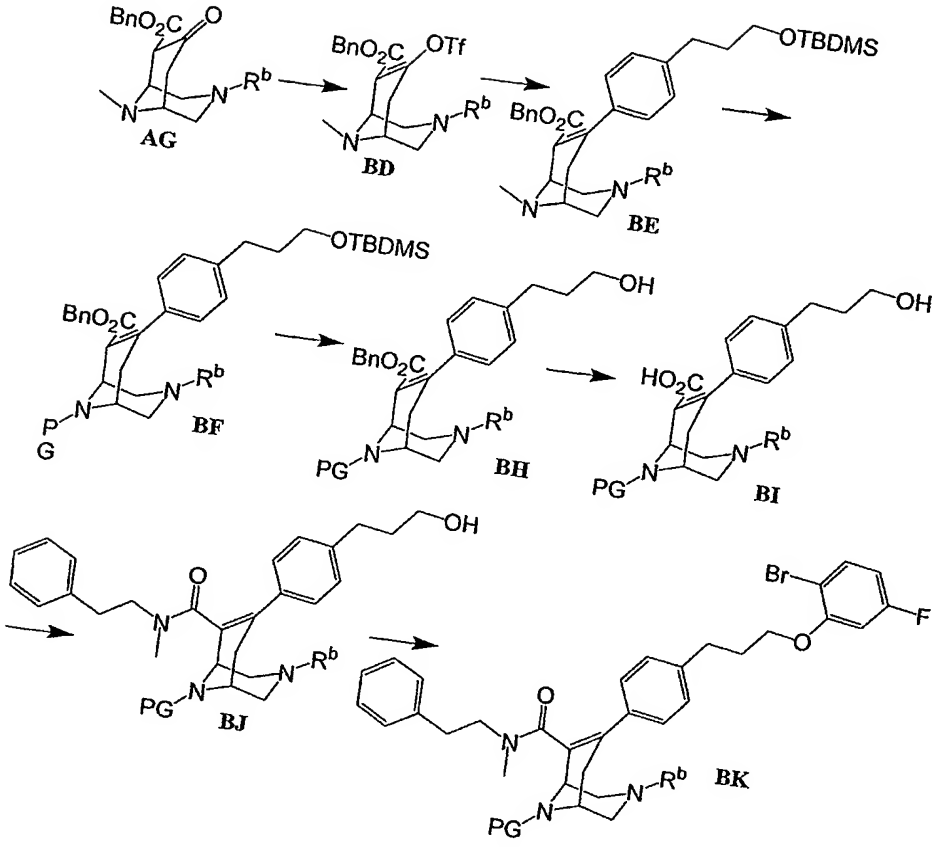


AD: R^b = Me
AE: R^b = Boc

AF: R^b = Boc, R^c = Me
AG: R^b = Boc, R^c = Bn

Finally precursor **BK** might be prepared as described in Scheme 26.

Scheme 26



Examples

General remarks

The compounds were characterized at least by LC-MS and ^{1}H-NMR. Only the LC-MS data are given here.

Abbreviations

AcCl	Acetyl chloride
ACE	Angiotensin Converting Enzyme
AcOH	Acetic acid
aq.	aqueous
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BSA	Bovine serum albumine
BuLi	*n*-Butyllithium
CDI	1,1-Carbonyldiimidazol
conc.	concentrated
DIBAL	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
DMAP	4-*N,N*-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
EDC·HCl	Ethyl-*N,N*-dimethylaminopropylcarbodiimide hydrochloride
EIA	Enzyme immunoassay
eq.	equivalent
Et	Ethyl
EtOAc	Ethyl acetate
FC	Flash Chromatography
HOBt	Hydroxybenzotriazol

KHMDS	Potassium hexamethyldisilazide
LAH	Lithium aluminium hydride
MeOH	Methanol
MPLC	Medium Pressure Liquid Chromatography
NMO	*N*-Methylmorpholine *N*-oxide
org.	organic
PG	protecting group
Ph	Phenyl
RP18	Reversed phase column, filled with C_{18} hydrocarbon
rt	room temperature
SEM	Trimethylsilylethoxymethyl
sol.	Solution
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
tBuOH	*tert*-Butanol
tBuOK	Potassium *tert*-butylate
Tf	Trifluoromethylsulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMAD	*N,N,N',N'*-Tetramethylazodicarboxamide

Preparation of the precursors

(*rac.*)-(*1R, *5S**)-9-Methyl-7-oxo-3,9-diazabicyclo[3.3.1]nonane-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (A)**

(4-Benzyl-6-ethoxycarbonylmethyl-1-methyl-piperazin-2-yl)acetic acid ethyl ester (Patent WO 92/05174) (71.0 g, 0.196 mol) was dissolved in MeOH (400 mL). TFA (77.8 mL, 1.02 mol) was added and the flask was purged with nitrogen. Pd/C (10%, 50% moisture, 3.6 g) was added. The flask was closed and purged

with hydrogen (3x). After 1 day, the mixture was filtered through *Celite* and washed with MeOH. The solvents were removed under reduced pressure and the foamy residue (92.7 g) was dried under high vacuum. A sol. of tBuOK (117.2 g, 1.04 mol) in toluene (3.07 L) was heated to reflux. A sol. of the crude piperazine formerly obtained, dissolved in THF (300 mL), was added dropwise over 50 min. The black mixture was stirred for 10 further min. and allowed to cool to rt. The mixture was cooled to 0 °C and AcOH (36.6 mL, 0.635 mol) was added. The solvents were removed under reduced pressure. This crude material was suspended in CH_2Cl_2 (400 mL) and cooled to 0 °C. DIPEA (19.1 mL, 112 mmol) was added. A sol. of Boc_2O (24.3 g, 113 mmol) in CH_2Cl_2 (200 mL) was added dropwise. The mixture was stirred for 1 h at 0 °C, then 1 h at rt. The mixture was washed with aq. 10% Na_2CO_3 (2x). The org. extracts were dried over $MgSO_4$, filtered and the solvents were evaporated under reduced pressure. The residue was purified by FC (EtOAc/heptane 1:1 → EtOAc). The title compound was obtained as oil (24.5 g, 38%). R_f = 0.05 (EtOAc/heptane 1:1) or 0.56 (MeOH/CH_2Cl_2 1:9). LC-MS: R_t = 2.94; ES+: 325.19.

(*rac.*)-(*1R, *5S**)-9-Methyl-7-trifluoromethanesulfonyloxy-3,9-diazabicyclo-[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (B)**

A sol. of bicyclononanone A (2.22 g, 6.80 mmol) in THF (50 mL) was cooled to 0 °C and NaH (about 60% in mineral oil, 326 mg, about 8.2 mmol) was added. A gas evolution was observed. After 20 min, Tf_2NPh (3.22 g, 9.00 mmol) was added. 10 min later, the ice bath was removed. After 3 h, the sol. was diluted with EtOAc and washed with brine (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by FC (EtOAc/heptane 3:1 → EtOAc) yielded the title compound as an oil (2.50 g, 80%). R_f = 0.15 (EtOAc/heptane 1:1). LC-MS: R_t = 4.73; ES+: 458.95.

Compounds of type C

3-(4-Bromophenyl)prop-1-yl 2-chlorophenyl ether (C1)

To a sol. of 3-(4-bromophenyl)propan-1-ol (Glover S. A., *et al.*; *Tetrahedron*, **1990**, *46*, 7247; 24.5 g, 0.114 mol) in toluene (600 mL) under nitrogen were added 2-chlorophenol (17.4 mL, 0.171 mmol), diisopropyl azodicarboxylate (33.1 mL, 0.171 mol) and tri-*n*-butylphosphine (42.2 mL, 0.171 mol). The sol. was heated to reflux and stirred under reflux overnight. The sol. was allowed to cool to rt and the solvents were removed under reduced pressure. The residue was diluted in EtOAc and washed with aq. 1M HCl (1x) and aq. 1M NaOH (2x). The org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC (petroleum ether → Et_2O/petroleum ether 1:99 → 1:19) led to the title compound (15.1 g, 41%). R_f = 0.70 (EtOAc/heptane 1:3).

2-(4-Bromophenyl)eth-1-yl 2,3,5-trimethylphenyl ether (C2)

A mixture of 2-(4-bromophenyl)ethanol (20.0 mL, 143 mmol), 2,3,5-trimethylphenol (31.1 g, 229 mmol), azodicarboxylic dipiperidide (72.1 g, 286 mmol) and tributylphosphine (88 mL; 357 mmol) in toluene (2.00 L) was heated to reflux for 2 h. The mixture was allowed to cool to rt. The mixture was filtered, washed with toluene and the solvents were partially removed under reduced pressure. The residue was diluted with Et_2O and washed with aq. 1M NaOH (2x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (petroleum ether → Et_2O/petroleum ether 1:3) yielded the title compound (33.1 g, 73%). LC-MS: R_t = 6.95.

1-Bromo-4-[3-(2-methoxybenzyl)propoxy]benzene (E)

4-Bromophenol (4.32 g, 25.0 mmol) and 1-(3-chloropropoxymethyl)-2-methoxy-benzene (Vieira E., *et al.*, *Bioorg. Med. Chem. Letters*, **1999**, *9*, 1397,4.88 g, 22.7 mmoL) were dissolved in DMF (150 mL). NaI (1.50 g, 0.10 mmol) and Cs_2CO_3

(16.3 g, 50.0 mmol) were added. The mixture was heated to 80 °C and stirred for 6 h, before it was allowed to cool to rt. After dilution with EtOAc (600 mL) the mixture was washed with water (1x), aq. 1M NaOH (1x). aq. 1M HCl (1x). The org. extracts were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue by FC (Et_2O/petroleum ether 1:9 → 1:4) yielded the title compound (5.66 g, 71%). R_f = 0.60 (Et_2O/heptane 1:1).

5-Bromo-2-[3-(2-methoxybenzyloxy)propoxy]pyridine (F)

3-(5-Bromopyridin-2-yloxy)propan-1-ol (Patent Application WO 98/39328, 1.05 g, 4.51 mmol) was diluted at rt in DMF (24 ml) and the sol. cooled to 0 °C. NaH (55 – 65 weight % in mineral oil, 193 mg, 4.42 – 5.23 mmol) was added and the yellow mixture was stirred for 20 min. 2-Methoxybenzyl chloride (1.49 ml, 10.7 mmol) was added and the solution was allowed to warm to rt and was stirred for 4 h. The mixture was quenched with ice and diluted with EtOAc (20 ml), washed with brine and water, dried over $MgSO_4$ and filtered. The solvents were evaporated under reduced pressure. Purification of the residue by FC (Et_2O, heptane 1:39 → 1:19) yielded the title compound (627 mg, 40 %) as an oil. R_f = 0.07 (Et_2O / heptane, 1:3).

Compounds of type G

(*rac.*)-(*1R, *5S**)-9-Methyl-7-[4-(2-trimethylsilanylethoxymethoxy)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (G1)**

A sol. of [2-(4-bromophenoxymethoxy)ethyl]trimethylsilane (Blass B. E., *et al.*, *Tetrahedron Lett.*, **2001**, *42*, 1611, 4.13 g, 13.6 mmol) in THF (30 mL) was cooled to –78 °C. BuLi (1.6 M in hexane, 9.1 mL, 14.6 mmol) was added. The sol. was stirred at –78 °C for 30 min. A sol. of $ZnCl_2$, prepared from $ZnCl_2$ (2.23 g, about 16.4 mmol) dried under high vacuum for 2 h at 140 °C and THF (35 mL),

was added and the resulting sol. was allowed to warm up to rt. A sol. of bicyclononene **B** (2.50 g, 5.45 mmol) in THF (5 mL) and then $Pd(PPh_3)_4$ (157 mg, 0.136 mmol) were added. After 10 min, the reaction mixture was heated to reflux. After 90 min, the reaction mixture was allowed to cool to rt and quenched with aq. 1M HCl. The mixture was diluted with EtOAc and washed with aq. 10% Na_2CO_3 (1x). The org. extracts were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue by FC ($MeOH/CH_2Cl_2$ 1:39 → 1:24 → 1:20) yielded the title compound as an oil (2.90 g, 99%). R_f = 0.39 ($MeOH/CH_2Cl_2$ 1:9). LC-MS: R_t = 4.35; ES+: 533.29.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (G2)**

A sol. of [2-(4-bromophenyl)ethoxy]-*tert*-butyldimethylsilane (Fuji K., *et al.*, *Tetrahedron Lett.*, **1990**, *31*, 6553, 21.8 g, 69.1 mmol) in THF (250 mL) was cooled to -78 °C. BuLi (1.55M in hexane, 44.6 mL, 69.1 mmol) was added. The sol. turned temporarily orange, then yellowish. After 30 min, $ZnCl_2$ (1M in THF, 70 mL, 70 mmol, prepared as described for **G1)** was added. The sol. was allowed to warm up to rt. Vinyl triflate **B** (12.91 g, 28.2 mmol) dissolved in THF (20 mL), and $Pd(PPh_3)_4$ (600 mg, 0.519 mmol) were added. The sol. was stirred at rt for 90 min and aq. 1M HCl (1 mL) was then added. The mixture was diluted in EtOAc and washed with aq. 1M NaOH (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC ($MeOH/CH_2Cl_2$ 1:49 → 1:24 → 3:47 → 2:25) yielded the title compound (10.91 g, 71%). R_f = 0.65 ($MeOH/CH_2Cl_2$ 1:9). LC-MS: R_t = 5.32; ES+: 545.49.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (G3)**

A sol. of [3-(4-bromophenyl)propoxy]-*tert*-butyldimethylsilane (Kiesewetter D. O., *Tetrahedron Asymmetry*, **1993**, *4*, 2183, 22.60 g, 68.6 mmol) in THF (250 mL) was cooled to -78 °C. BuLi (1.55M in hexane, 44.3 mL, 68.6 mmol) was added. The sol. turned orange, then dark green. After 30 min, $ZnCl_2$ (1M in THF, 69 mL, 69 mmol, prepared as described for **G2**) was added, whereas the sol. turned deep yellow. The mixture was allowed to warm up to rt. Vinyl triflate **B** (12.91 g, 28.2 mmol) in THF (20 mL) and then $Pd(PPh_3)_4$ (600 mg, 0.519 mmol) were added. The mixture was stirred at rt for 90 min and aq. 1M HCl (1 mL) was added. The mixture was diluted with EtOAc and washed with aq. 1M NaOH (1x). The org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC ($MeOH/CH_2Cl_2$ 1:49 → 1:24 → 3:47 → 2:23) yielded the title product (10.76 g, 70%). R_f = 0.60 ($MeOH/CH_2Cl_2$ 1:9). LC-MS: R_t = 4.95; ES+: 559.51.

(*rac.*)-(*1R, *5S**)-7-{6-[3-(2-Methoxybenzyloxy)propoxy]pyridin-3-yl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (G4)**

A sol. of bromopyridinyl derivative **F** (300 mg, 852 μmol) in THF (10 ml) was cooled to –78 °C. BuLi (1.55M in hexane, 0.580 ml, 889 μmol) was added and the mixture was stirred for 30 min. $ZnCl_2$ (1M in THF, 0.94 ml, 0.94 mmol, prepared as described for **G2**) was added and the reaction mixture was allowed to warm up to rt. Vinyl triflate **B** (259 mg, 596 μmol) in THF (1 ml), was added, followed by $Pd(PPh_3)_4$ (20.4 mg, 16.6 μmol). The mixture was refluxed for 2 h. The reaction was terminated upon addition of ice. After dilution with EtOAc (125 ml), the reaction mixture was washed with 10% aq. Na_2CO_3 and the org. extracts were dried over $MgSO_4$ and filtered. The solvents were evaporated under reduced pressure. Purification of the residue by FC (CH_2Cl_2/MeOH: 39:1 → 29:1 → 24:1 → 19:1 → 9:1) led to title compound (197 mg, 54 %). R_f = 0.35 (CH_2Cl_2/MeOH 9:1). LC-MS: R_t = 4.06; ES+: 582.78.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Methoxybenzyloxy)propoxy]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (G5)**

A sol. of bromophenyl derivative **E** (5.60 g, 15.9 mmol) in THF (50 mL) was cooled to -78 °C. BuLi (1.55M in hexane, 10.3 mL, 15.9 mmol) was added. The sol. was stirred at -78 °C for 30 min and $ZnCl_2$ (1M in THF, 17.5 mL, 17.5 mmol, prepared as described for **G2**) was added. After warming up to rt, a sol. of vinyl triflate **B** (3.63 g, 7.90 mmol) in THF (5 mL), followed by $Pd(PPh_3)_4$ (205 mg, 0.177 mmol), were added. The mixture was heated to reflux while turning black. After 1 h, the reaction mixture was allowed to cool to rt. Ice was added and the mixture was diluted in EtOAc. The org. extracts were washed with aq. 1M NaOH (1x) and dried over $MgSO_4$. The solvents were removed under reduced pressure. Purification of the residue by FC ($MeOH/CH_2Cl_2$ 1:49 → 3:97 → 1:24 → 1:19 → 1:9) yielded the title compound (4.57 g, 99%). R_f = 0.50 ($MeOH/CH_2Cl_2$ 1:9). LC-MS: R_t = 4.17; ES+: 581.60.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Chlorophenoxy)propyl]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (G6)**

A sol. of bromophenyl derivative **C1** (16.0 g, 49.0 mmol) in THF (700 mL) was cooled to -78 °C. BuLi (1.55M in hexane, 34.8 mL, 54.0 mmol) was added. The sol. was stirred at -78 °C for 30 min and $ZnCl_2$ (1M in THF, 54.0 mL, 54.0 mmol, prepared as described for **G2**) was added. After warming up to rt, a sol. of vinyl triflate **B** (15.0 g, 32.7 mmol) in THF (50 mL), followed by $Pd(PPh_3)_4$ (945 mg, 0.818 mmol), were added. The sol. was heated to reflux. After 30 min, the reaction mixture was allowed to cool to rt. Ice was added and the mixture was diluted in EtOAc. The org. phase was washed with aq. 1M NaOH (1x) and dried over $MgSO_4$. The solvents were removed under reduced pressure. Purification of the residue by FC ($MeOH/CH_2Cl_2$ 1:49 → 3:97 → 1:24 → 1:19 → 1:9) yielded the title compound (10.5 g, 58%). LC-MS: R_t = 4.41; ES+: 555.13.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (G7)**

BuLi (1.6 M in hexane, 218 mL, 350 mmol) was added to a sol. of [2-(4-bromophenoxy)ethoxy]-*tert*-butyldimethylsilane (Morita, C.; et al.al.; *Heterocycles*, **2000**, *52*, 1163; 129 g, 342 mmol) in THF (1.0 L) at -78 °C. The mixture was stirred for 1 h at –78 °C, and $ZnCl_2$ (1M in THF, 400 mL, 400 mmol, prepared as described for **G2**) was added. The mixture was allowed to warm up to rt. Bicyclononene **B** (78.4 g, 171 mmol) and $Pd(PPh_3)_4$ (4.94 g, 4.28 mmol) were added. The mixture was heated to reflux for 0.5 h, and was allowed to cool to rt. Aq. 1M HCl (2 mL) was added. The mixture was diluted with EtOAc (2 L) and washed with aq. 1M NaOH (750 mL). The aq. extracts were extracted back with EtOAc (1x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC ($MeOH/CH_2Cl_2$ 1:49 → 1:24 → 3:47 → 2:23) yielded the title compound (87.7 g, 91%). R_f = 0.60 (MeOH/CH2Cl2 1:9). LC-MS: R_t = 4.74; ES+: 561.41.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (G8)**

BuLi (1.5 M in hexane, 13.4 mL, 20 mmol) was added to a sol. [2-(4-bromophenyl)ethoxy]-*tert*-butyldiphenylsilane (8.79 g, 20.0 mmol, prepared from 2-(4-bromophenyl)ethanol, TBDPS-Cl and imidazol in DMF) in THF (40 mL) at -78 °C. The mixture was stirred for 30 min at –78 °C, and $ZnCl_2$ (1M in THF, 24 mL, 24 mmol, prepared as described for **G2**) was added. The mixture was allowed to warm up to rt. Bicyclononene **B** (3.67 g, 8.00 mmol) and $Pd(PPh_3)_4$ (231 mg, 0.20 mmol) were added. The mixture was heated to 40 °C for 40 min, and was allowed to cool to rt. Aq. 1M HCl (2 mL) was added. The mixture was diluted with EtOAc and washed with aq. 1M NaOH. The aq. extracts were extracted back with

EtOAc (1x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC ($MeOH/CH_2Cl_2$ 1:49 → 1:24 → 3:47 → 2:23) yielded the title compound (4.32 g, 81%). LC-MS: R_t = 1.06; ES+: 669.49.

Compounds of type H

(*rac.*)-(*1R*, 5S)-7-[4-(2-Trimethylsilanylethoxymethoxy)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (H1)**

β,β,β--Trichloro-*tert*-butyl chloroformate (6.60 g, 27.5 mmol) was added to a sol. of bicyclononene **G1** (2.93 g, 5.50 mmol) in 1,2-dichloroethane (60 mL). The sol. was heated to reflux. After 3 h, the reaction mixture was allowed to cool to rt, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 1:3 → 2:3 → 1:1) yielded the title compound as an oil (3.31 g, 83%). R_f = 0.52 (EtOAc/heptane 1:1). LC-MS: R_t = 7.40; ES+: 742.52.

(*rac.*)-(*1R*, 5S)-7-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (H2)**

As for the preparation of compound **H1**, from bicyclononene **G2** (10.91 g, 20.0 mmol), β,β,β-trichloro-*tert*-butyl chloroformate (24.0 g, 100 mmol), and 1,2-dichloroethane (210 mL). Purification of the residue FC (EtOAc/heptane 1:9 → 1:4 →2:3) yielded the title compound (13.75 g, 94%). R_f = 0.64 (EtOAc/heptane 1:1). LC-MS: R_t = 7.66; ES+: 755.37.

(*rac.*)-(*1R*, 5S)-7-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (H3)**

As for the preparation of compound **H1**, from bicyclononene **G3** (10.96 g, 19.6 mmol), β,β,β-trichloro-*tert*-butyl chloroformate (23.5 g, 98.1 mmol), and 1,2-dichloroethane (210 mL). Purification of the residue by FC (EtOAc/heptane 1:9 → 1:4 → 2:3) yielded the title compound (13.50 g, 92%). R_f = 0.58 (EtOAc/heptane 1:1). LC-MS: R_t = 7.79; ES+: 769.49.

(*rac.*)-(*1R, *5S**)-7-{6-[3-(2-Methoxybenzyloxy)propoxy]pyridin3-yl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (H4)**

As for the preparation of compound **H1**, from bicyclononene **G4** (373 mg, 0.642 mmol), β,β,β-trichloro-*tert*-butyl chloroformate (770 mg, 3.11 mmol), and 1,2-dichloroethane (8 mL). Purification of the residue by FC (EtOAc/heptane 1:9 → 1:4 → 1:3) yielded the title compound (382 mg, 77%). R_f = 0.47 (EtOAc/heptane 1:1). LC-MS: R_t = 7.14; ES+: 770.50.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Methoxybenzyloxy)propoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (H5)**

As for the preparation of compound **H1**, from bicyclononene **G5** (4.57 g, 7.87 mmol), β,β,β-trichloro-*tert*-butyl chloroformate (9.44 g, 39.4 mmol), and 1,2-dichloroethane (100 mL). Purification of the residue by FC (EtOAc/heptane 1:9 → 1:4 → 1:1) yielded the title compound (5.35 g, 88%). R_f = 0.46 (EtOAc/heptane 1:1).

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Chlorophenoxy)propyl]phenyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (H6)**

As for the preparation of compound **H1**, from bicyclononene **G6** (10.51 g, 18.9 mmol), β,β,β-trichloro-*tert*-butyl chloroformate (22.7 g, 94.7 mmol), and 1,2-

dichloroethane (350 mL). Purification of the residue by FC (EtOAc/heptane 1:8 → 1:4 → 1:1) yielded the title compound (12.5 g, 88%).

(*rac.*)-(*1R, *5S**)-7-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (H7)**

As for the preparation of compound **H1**, from bicyclononene **G7** (87.7 g, 156 mmol), β,β,β-trichloro-*tert*-butyl chloroformate (188 g, 784 mmol), and 1,2-dichloroethane (1.75 L). Purification of the residue by FC (EtOAc/heptane 1:19 → 1:3) yielded the title compound (111 g, 95%). R_f = 0.75 (EtOAc/heptane 1:1). LC-MS: R_t = 7.84.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (H8)**

As for the preparation of compound **H1**, from bicyclononene **G8** (4.32 g, 6.46 mmol), β,β,β-trichloro-*tert*-butyl chloroformate (7.75 g, 32.3 mmol), and 1,2-dichloroethane (100 mL). Purification of the residue by FC (EtOAc/heptane 1:19 → 1:3) yielded the title compound (4.97 g, 90%). R_f = 0.75 (EtOAc/heptane 1:1). LC-MS: R_t = 1.35.

Compounds of type J

(*rac.*)-(*1R, *5S**)-6-Hydroxymethyl-7-[4-(2-trimethylsilanylethoxymethoxy)-phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3, 9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (J1)**

A sol. of bicyclononene **H1** (3.31 g, 4.58 mmol) in CH_2Cl_2 (60 mL) was cooled to –78 °C. DIBAL (1M in toluene, 10.1 mL, 10.1 mmol) was added. The sol. was stirred for 30 min at –78 °C and was then allowed to warm slowly. DIBAL (5

mL) was added again after 1.5 h (-65 °C). Later, DIBAL was added successively in 5 mL-portions until TLC displayed no more starting material. Ice and water were then added at –50 °C. The cold bath was removed and the mixture warmed slowly to rt. More CH_2Cl_2 was added and the mixture was washed with aq. 1M HCl. The aq. phase was extracted with CH_2Cl_2 (1x) and the combined org. extracts were dried over $MgSO_4$. After filtration and evaporation of the solvents under reduced pressure, the residue was purified by FC (EtOAc/heptane 1:4 → 1:3 → 2:3) to yield the title compound as an oil (1.89 g, 60%). R_f = 0.50 (EtOAc/heptane 1:1). LC-MS: R_t = 7.08; ES+: 661.38, 702.83.

(*rac.*)-(*1R, *5S**)-7-{4-2-(*tert*-Butyldimethylsilanyloxy)ethyl]phenyl}-6-hydroxymethyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (J2)**

To a sol. of bicyclononene **H2** (1.57 g, 2.32 mmol) in CH_2Cl_2 (40 mL) at -78 °C DIBAL (1M in toluene, 5.80 mL, 5.80 mmol) was added. The sol. was stirred at -78 °C for 1 h. Ice was added, and the mixture was allowed to warm up to rt. More CH_2Cl_2 was added and the org. extracts were washed with aq. 1M HCl (1x), dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:3) yielded the title compound (868 mg, 59%). LC-MS: R_t = 7.38; ES+: 715.48.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-6-hydroxymethyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (J3)**

A sol. of bicyclononene **H3** (2.39 g, 3.20 mmol) in CH_2Cl_2 (55 mL) was cooled to -78 °C. DIBAL (1M in toluene, 8.00 mL, 8.00 mmol) was added and the mixture was stirred at -78 °C for 1 h. Ice was added, and the mixture was allowed to warm up to rt. More CH_2Cl_2 was added and the org. extracts were washed with aq. 1M HCl (1x), dried over $MgSO_4$ and filtered. The solvents were removed under

reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:3) yielded the title compound (1.34 g, 59%). LC-MS: R_t = 7.59; ES+: 727.54.

(*rac.*)-(*1R, *5S**)-6-Hydroxymethyl-7-{6-[3-(2-methoxybenzyloxy)propoxy]-pyridin-3-yl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (J4)**

A sol. of bicyclononene **H4** (345 mg, 0.447 mmol) in CH_2Cl_2 (10 mL) was cooled to -78 °C. DIBAL (1M in toluene, 1.92 mL, 1.92 mmol) was added. The mixture was stirred at -78 °C for 1 h and again two portions of DIBAL (0.50 mL, 0.50 mmol) were added successively. After 2 h, ice was added. The mixture was allowed to warm up to rt and was diluted with more CH_2Cl_2. The org. extracts were washed with aq. 10% Na_2CO_3 (2x), dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 1:3 → 2:3 → 3:1) yielded the title compound (122 mg, 37%). R_f = 0.36 (EtOAc/heptane 1:1). LC-MS: R_t = 6.51; ES+: 728.49.

(*rac.*)-(*1R, *5S**)-6-Hydroxymethyl-7-(4-hydroxyphenyl)-3,9-diazabicyclo-[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (K)**

To a sol. of bicyclononene **J1** (1.89 g, 2.79 mmol) in THF/MeOH (1:1, 20 mL), a sol. of conc. H_2SO_4 (0.100 mL) in MeOH (10 mL) was added. The mixture was stirred for 3 h at rt. The reaction mixture was diluted with EtOAc, washed with brine (1x) and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Crystallization of the residue from EtOAc/heptane led to the title compound (1.03 g, 67%). R_f = 0.14 (EtOAc/heptane 1:1). LC-MS: R_t = 5.17; ES-: 547.06.

(*rac.*)-(*1R, *5S**)-6-Hydroxymethyl-7-{4-[3-(2-methoxybenzyloxy)propoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (L)**

To a sol. of bicyclononene **K** (1.03 g, 1.87 mmol) in DMF (20 mL) were added NaI (280 mg, 1.87 mmol), Cs_2CO_3 (609 mg, 1.87 mmol) and then 1-(3-chloropropoxymethyl)-2-methoxybenzene (Vieira E., *et al.*, *Bioorg. Med. Chem. Letters*, **1999**, *9*, 1397, 400 mg, 1.87 mmol). The mixture was stirred at 100 °C. After 1.5 h, another portion of Cs_2CO_3 (609 mg, 1.87 mmol) and 1-(3-chloropropoxymethyl)-2-methoxybenzene chloride (400 mg, 1.87 mmol) were added to complete the reaction. After 1.5 h later, the mixture was allowed to cool to rt and diluted with EtOAc. The org. extracts were washed with brine (1x). The org. extracts were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 1:3 → 2:3) yielded the title compound (1.00 g, 73%). R_f = 0.35 (EtOAc/heptane 1:1). LC-MS: R_t = 6.54.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Methoxybenzyloxy)propoxy]phenyl}-6-[2-(2-methoxyphenyl)acetoxymethyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (M)**

To a sol. of bicyclononene **L** (500 mg, 0.687 mmol) in CH_2Cl_2 (10 mL) were added (2-methoxyphenyl)acetic acid (206 mg, 1.37 mmol), DMAP (cat. amount), DIPEA (0.230 mL, 1.34 mmol) and EDC·HCl (134 mg, 0.700 mmol). The sol. was stirred at rt for 90 min, when a second portion of DIPEA (0.100 mL, 0.584 mmol) was added. After 3 h, the reaction mixture was diluted in more CH_2Cl_2 and washed with water (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 1:3 → 2:3) yielded the title compound (495 mg, 82%). R_f = 0.42 (EtOAc/heptane 1:1). LC-MS: R_t = 7.33; ES+: 897.33.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Methoxybenzyloxy)propoxy]phenyl}-6-[2-(2-methoxyphenyl)acetoxymethyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (N)**

A mixture of CH_2Cl_2 (3 mL) and HCl/dioxane (4M, 1 mL) was slowly added to bicyclononene **M** (495 mg, 0.585 mmol) in an ice bath. The resulting sol. was stirred at 0 °C. After 1 h, HCl/dioxane (4M, 0.5 mL) was added, and 1 h later the ice bath was removed. After 75 min, the solvents were removed under reduced pressure and the residue dried under high vacuum. The resulting foam was estimated to contain about 80% of the title compound according to LC-MS and was used without further purification. LC-MS: R_t = 4.97; ES+: 774.97.

(*rac.*)-(*1R, *5S**)-6-[2-(2-Methoxyphenyl)acetoxymethyl]-7-{6-[3-(2-methoxybenzyloxy)propoxy]pyridin-3-yl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (O)**

To a sol. of bicyclononene **J4** (122 mg, 0.167 mmol) in CH_2Cl_2 (5 mL) were added (2-methoxyphenyl)acetic acid (50 mg, 0.328 mmol), DIPEA (0.126 mL, 0.740 mmol), DMAP (cat. amount) and EDC·HCl (34 mg, 0.173 mmol). The mixture was stirred at rt for 3 h, then diluted in CH_2Cl_2, and washed with washed with water (1x). The org. extracts were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 1:3 → 2:3 → 1:1) yielded the title compound (108 mg, 74%). LC-MS: R_t = 7.34; ES+: 876.54.

(*rac.*)-(*1R, *5S**)-7-{6-[3-(2-Methoxybenzyloxy)propoxy]pyridin-3-yl}-6-[2-(2-methoxyphenyl)acetoxymethyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester dihydrochloride salt (P)**

Bicyclononene **O** (114 mg, 0.130 mmol) was dissolved in CH_2Cl_2 (2 mL). The sol. was cooled to -40 °C and 4M HCl/dioxane (2 mL) was added. The sol. was stirred for 50 min while warming up slowly to 0 °C and then stirred for 1.5 h at 0 °C. The solvents were rapidly removed under reduced pressure. The residue was dried under high vacuum to give the title compound (156 mg) as a foam that was used without further purification. LC-MS: R_t = 4.86; ES+: 776.48.

Compounds of type Q

(*rac.*)-(*1R, *5S**)-7-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]phenyl}-6-[2-(2-methoxyphenyl)acetoxymethyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (Q1)**

To a sol. of bicyclononene **J2** (868 mg, 1.25 mmol) in CH_2Cl_2 (20 mL) were added (2-methoxyphenyl)acetic acid (343 mg, 2.06 mmol), DIPEA (0.652 mL, 3.81 mmol), DMAP (cat. amount), and EDC·HCl (201 mg, 1.05 mmol). The mixture was stirred at rt for 1 h and EDC·HCl (73 mg, 0.38 mmol) and DIPEA (0.163 mmol, 0.952 mmol) were added again. After 30 min. the reaction mixture was diluted with CH_2Cl_2, washed with aq. 1M HCl (1x), and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:3) yielded the title compound (948 mg, 90%). LC-MS: R_t = 7.98; ES+: 861.51.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-6-[2-(2-methoxyphenyl)acetoxymethyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (Q2)**

To a sol. of bicyclononene **J3** (1.34 g, 1.90 mmol) in CH_2Cl_2 (30 mL), were added 2-methoxyphenylacetic acid (633 mg, 3.81 mmol), DIPEA (0.652 mL, 3.81 mmol), DMAP (cat. amount), and EDC·HCl (402 mg, 2.09 mmol). The sol. was stirred at rt for 1 h and EDC·HCl (73 mg, 0.38 mmol) and DIPEA (0.163 mmol, 0.952 mmol) were added again. After 30 min., the reaction mixture was diluted with CH_2Cl_2, washed with aq. 1M HCl (1x) and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:3) yielded the title compound (1.47 g, 90%). LC-MS: R_t = 8.17; ES+: 875.53.

Compounds of type R

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-[4-(2-hydroxyethyl)phenyl]-6-[2-(2-methoxy-phenyl)acetoxymethyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (R1)**

Bicyclononene **Q1** (948 mg, 1.13 mmol) was dissolved in CH_2Cl_2 (20 mL). The sol. was cooled to 0 °C and 4M HCl/dioxane (20 mL) was added. After 2.25 h the solvents were rapidly removed under reduced pressure, and the residue was immediately dried under high vacuum. The resulting foam was then dissolved in THF (55 mL) and cooled to -78 °C. DIPEA (0.774 mL, 4.51 mmol) and DMAP (cat. amount) were added, followed by the addition of acetyl chloride (0.064 mL, 0.91 mmol). After 2.5 h at -78 °C, MeOH (20 mL) was added, and the reaction mixture was allowed to warm to rt. The reaction mixture was diluted in EtOAc, washed with aq. 1 M HCl (1x), and the org. extract were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:2) yielded the title compound (651 mg, 55%). LC-MS: R_t = 5.47; ES+: 689.05.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-[4-(3-hydroxypropyl)phenyl]-6-[2-(2-methoxy-phenyl)acetoxymethyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (R2)**

To a sol. of bicyclononene **Q2** (1.47 g, 1.72 mmol) in CH_2Cl_2 (25 mL), 4M HCl/dioxane (25 mL) was added at 0 °C. After 2.25 h at 0 °C the solvents were rapidly removed under reduced pressure, and the residue was immediately dried under high vacuum. The resulting foam was then dissolved in THF (75 mL) and cooled to -78 °C. DIPEA (1.18 mL, 6.88 mmol) and DMAP (cat. amount) were added, followed by slow addition of acetyl chloride (0.098 mL, 1.38 mmol). After 2.5 h at - 78 °C MeOH (80 mL) was added, and the reaction mixture was allowed to warm up to rt. After dilution with EtOAc, the mixture was washed with aq. 1 M HCl (1x) and the org. extracts were dried over $MgSO_4$ and filtered. The

solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:2) yielded the title compound (651 mg, 55%).

Compounds of type S

(*rac.*)-(*1R*, 5S)-3-Acetyl-7-{4-[3-(2-methoxybenzyloxy)propoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (S1)**

A sol. of bicyclononene **H5** (5.35 g, 6.95 mmol) in CH_2Cl_2 (30 mL) was cooled to 0°C. 4M HCl/dioxane (30 mL) was added. The sol. was stirred at 0 °C for 3.5 h, the solvents were removed under reduced pressure and the residue dried at high vacuum. The resulting foam was dissolved in THF (100 mL) and cooled to -78 °C. DIPEA (5.80 mL, 34.7 mmol) was added. A sol. of acetyl chloride (0.494 mL, 6.95 mmol) in THF (10 mL) was added slowly. The reacton mixture was stirred at -78 °C for 90 min, then allowed allowed to warm to rt and diluted in MeOH (5 mL), then in EtOAc. The org. extracts were washed with aq. 1M HCl (2x), aq. sat. $NaHCO_3$ (1x), dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 1:3 → 1:1 → EtOAc) yielded the title compound (3.67 g, 74%). R_f = 0.50 (EtOAc). LC-MS: 6.22; ES+: 711.31.

(*rac.*)-(*1R*, 5S)-3-Acetyl-7-{4-[3-(2-chlorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (S2)**

As for compound **S1**, from **H6** (10.8 g, 14.5 mmol), CH_2Cl_2 (110 mL), 4M HCl/dioxane (110 mL), THF (220 mL), DIPEA (12.4 mL, 72.6 mmol), DMAP (89 mg, 0.73 mmol), acetyl chloride (1.24 mL, 17.4 mmol), and MeOH (5 mL). Purification of the residue by FC (EtOAc/heptane 1:3 → 1:1 → EtOAc) yielded the title compound (8.59 g, 86%). R_f = 0.43 (EtOAc). LC-MS: 6.32; ES+: 684.99.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-[4-(2-hydroxyethyl)phenyl]-3,9-diazabicyclo-[3.3.1]non-6-ene-6,9-dicarboxylic acid 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (S3)**

As for compound **S1**, from **H2** (3.00 g, 4.08 mmol), CH_2Cl_2 (30 mL), 4M HCl/dioxane (30 mL), THF (60 mL), DMAP (25 mg, 0.204 mmol), DIPEA (2.74 mL, 16.4 mmol), acetyl chloride (0.343 mL, 4.08 mmol), and MeOH (5 mL). Purification of the residue by FC (EtOAc/heptane 1:1 → EtOAc → MeOH/EtOAc 1:9) led to the title compound (1.80 g, 79%). R_f = 0.20 (EtOAc).

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-[4-(2-hydroxyethoxy)phenyl]-3,9-diazabicyclo-[3.3.1]non-6-ene-6,9-dicarboxylic acid 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (S4)**

As for compound **S1**, from **H7** (5.80 g, 7.73 mmol), CH_2Cl_2 (60 mL), 4M HCl/dioxane (60 mL), THF (50 mL), DMAP (47 mg, 0.384 mmol), DIPEA (5.29 mL, 31.7 mmol), acetyl chloride (0.604 mL, 8.08 mmol), and MeOH (5 mL). Purification of the residue by FC (EtOAc/heptane 1:1 → EtOAc → MeOH/EtOAc 1:9) led to the title compound (3.07 g, 69%). R_f = 0.20 (EtOAc). LC-MS: R_t = 4.80; ES+: 576.93.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-[4-(3-hydroxypropyl)phenyl]-3,9-diazabicyclo-[3.3.1]non-6-ene-6,9-dicarboxylic acid 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (S5)**

As for compound **S1**, from **H3** (5.04 g, 6.74 mmol), CH_2Cl_2 (80 mL), 4M HCl/dioxane (80 mL), THF (80 mL), without DMAP, DIPEA (4.62 mL, 27.0 mmol), acetyl chloride (0.430 mL,6.06 mmol), and MeOH (5 mL). Purification of the residue by FC (EtOAc/heptane 1:1 → EtOAc → MeOH/EtOAc 1:9) led to the title compound (3.23 g, 83%). R_f = 0.20 (EtOAc). LC-MS: R_t = 1.00; ES+: 575.13.

Compounds of type T

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-{4-[3-(2-methoxybenzyloxy)propoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (T1)**

To a sol. of bicyclononene **S1** (3.67 g, 5.15 mmol) in EtOH (27 mL) was added aq. NaOH (1M, 27 mL, 27 mmol). The mixture was heated to 80 °C for 3 h and then allowed to cool to rt. After adjustment of the pH to 1-2 with aq. 1M HCl and extraction with EtOAc (2x), the combined org. extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:1 → 3:1 → EtOAc → MeOH/EtOAc 1:9) yielded the title compound (1.45 g, 41%). LC-MS: R_t = 5.50; ES+: 683.24.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-{4-[3-(2-chlorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (T2)**

From bicyclononene **S2** (8.59 g, 12.5 mmol) the title compound (4.29 g, 52%) was obtained after purification by FC ($MeOH/CH_2Cl_2$ 1:99 → 1:49 → 3:97 → 1:24) as described for **T1**. LC-MS: R_t = 5.61; ES-: 655.24.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-[4-(2-hydroxyethoxy)phenyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (T3)**

From bicyclononene **S4** (3.07 g, 5.73 mmol) in EtOH (119 mL) and aq. 1M NaOH (119 mL) the title compound (1.88 g, 60%) was obtained after purification by FC ($MeOH/CH_2Cl_2$ 1:99 → 1:49 → 3:97 → 1:24) as described for **T1**. LC-MS: R_t = 4.32; ES+: 548.96.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-{4-[3-(*tert*-butyldimethylsilanyloxy)propyl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (T4)**

A mixture of bicyclononene **AZ1** (1.60 g, 2.93 mmol), imidazol (797 mg, 11.7 mmol) and TBDMS-Cl (1.1 g, 7.30 mmol) in DMF (20 mL) was stirred at rt overnight. Aq. sat. NH_4Cl was added and the mixture was extracted with hexane (3x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were evaporated under reduced pressure. A mixture of this crude product and K_2CO_3 (0.2 g) in THF (30 ml), MeOH (10 ml), and H_2O (10 ml) was stirred at rt for 3 h. Aq. sat. NH_4Cl was added and this mixture was extracted with Et_2O (3x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. This yielded the title compound (1.85 g, 95%) that was used withour further purification.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (T5)**

As for compound **T4**, but from bicyclononene **AZ2** (crude, about 5.79 mmol), imidazol (1.2 g, 17.6 mmol) and TBDPS-Cl (4.84 g, 17.6 mmol) in DMF (50 mL), then K_2CO_3 (0.5 g), THF (60 mL), MeOH (20 mL), and H_2O (20 mL). The crude title compound (9.6 g, quantitative yield) was used further without purification. LC-MS: R_t = 1.26.

Compounds of type U

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-(4-hydroxyphenyl)-6-(methylphenethylcarbamoyl)-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (U1)**

To a sol. of bicyclononene **W1** (0.93 g, 1.37 mmol) in CH_2Cl_2 (10 mL) was added HCl/dioxane (10 mL) at 0 °C. After 15 min, the ice bath was removed. The reaction mixture was stirred at rt for 1 h and the solvents were removed under reduced pressure. After drying at high vacuum for 30 min., the resulting solid or foam was dissolved in THF (10 mL). DIPEA (0.983 mL, 5.48 mmol) and DMAP (cat. amount) were added. The sol. was cooled to -78 °C and a sol. of AcCl (0.0973 mL, 1.37 mmol) in THF (5 mL) was slowly added over 2 min. After 75 min at -78 °C MeOH (10 mL) was added and the mixture was allowed to warm up. After dilution in EtOAc, the reaction mixture was washed with aq. 1M HCl (1x) and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:3 → 1:1 → 3:1 → EtOAc → MeOH/EtOAc 1:19 → 1:9) yielded the title compound (253 mg, 30%). R_f = 0.30 (EtOAc). LC-MS: R_t = 5.12; ES+: 622.31.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-[4-(2-hydroxyethyl)phenyl]-6-(methylphenethyl-carbamoyl)-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (U2)**

To a sol. of bicyclononene **W2** (3.46 g, 4.88 mmol) in CH_2Cl_2 (35 mL) was added HCl (4M in dioxane, 35 mL) at 0 °C. After 1 h the ice bath was removed, and stirring continued for 1 h at rt. The solvents were removed under reduced pressure and the residue dried under high vacuum. The resulting foam was dissolved in THF (50 mL). DIPEA (3.34 mL, 19.5 mmol) and DMAP (cat. amount) were added. The reaction mixture was cooled to -78 °C and AcCl (0.347 mL, 4.88 mmol) in THF (20 mL) was added dropwise. After 2 h at -78 °C, AcCl (0.100 mL, 1.41 mmol) was added again, followed by a third portion of AcCl (0.050 mL, 0.71 mmol) 1.5 h later. MeOH (10 mL) was added after 30 min. and the mixture was allowed to warm up to rt. After dilution with EtOAc and washing with aq. 1M HCl (1x) and aq. sat. $NaHCO_3$ (1x), the org. extracts were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:1 → EtOAc → MeOH/EtOAc

1:9) yielded the title compound as a colorless foam (2.06 g, 65%). R_f = 0.15 (EtOAc). LC-MS: R_t = 5.14; ES+: 650.21.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-[4-(3-hydroxypropyl)phenyl]-6-(methylphenethylcarbamoyl)-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (U3)**

To a sol. of bicyclononene **W3** (3.18 g, 4.40 mmol) in CH_2Cl_2 (30 mL) was added HCl (4M in dioxane, 30 mL) at 0 °C. After 1 h at 0 °C and 1 h at rt, the solvents were removed under reduced pressure and the residue dried under high vacuum. The residue was dissolved in THF (45 mL), and DIPEA (3.02 mL, 17.6 mmol) and DMAP (cat. amount) were added. The sol. was cooled to -78 °C and a sol. of AcCl (0.313 mL, 4.40 mmol) in THF (15 mL) was added dropwise over 5 min. After 1.25 h, AcCl (0.070 mL, 0.984 mmol) was added again. After 30 min. MeOH (10 mL) was added and the mixture was allowed to warm up to rt. After dilution in EtOAc and washing with aq. 1M HCl (1x) and aq. sat. $NaHCO_3$ (1x), the org. extracts were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:1 → EtOAc → MeOH/EtOAc 1:9) yielded the title compound (2.92 g, 66%) as a foam. R_f = 0.23 (EtOAc). LC-MS: R_t = 5.24; ES+: 664.29.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-[4-(2-hydroxyethoxy)phenyl]-6-(methylphenethylcarbamoyl)-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (U4)**

A mixture of bicyclononene **T3** (1.88 g, 3.42 mmol), methylphenethylamine (1.49 mL, 10.3 mmol), DMAP (41 mg, 0.34 mmol), DIPEA (2.33 mL, 18.0 mmol), HOBt (46 mg, 0.34 mmol) and EDC·HCl (1.64 g, 8.55 mmol) in $CHCl_3$ (40 mL) was stirred overnight at rt. The mixture was diluted in CH_2Cl_2 and washed with aq. 1M HCl (2x) and aq. sat. $NaHCO_3$. The organic extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure.

Purification of the residue by FC (EtOAc/ heptane 1:4 → 1:1 → 4:1 → EtOAc) yielded the title compound (1.33 g, 58%). LC MS: R_t = 5.25; ES+: 666.08.

Compounds of type V

(*rac.*)-(*1R, *5S**)-7-(4-Hydroxyphenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (V1)**

To a sol. of bicyclononene **H1** (4.18 g, 5.79 mmol) in EtOH (55 mL) aq. NaOH (1M, 55 mL, 55 mmol) was added. The mixture was stirred at 80 °C for 28 h before it was allowed to cool to rt and acidified to pH 1 with aq. 1M HCl. After extraction with EtOAc (3x) the combined org. extracts were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue by FC ($MeOH/CH_2Cl_2$ 1:49 → 3:97 → 1:24 → 1:19 → 1:9 → 1:4) yielded the title compound (1.50 g, 40%). R_f = 0.29. LC-MS: R_t = 4.91; ES-: 561.12.

(*rac.*)-(*1R, *5S**)-7-[4-(2-Hydroxyethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (V2)**

To a sol. of bicyclononene **H2** (13.75 g, 18.7 mmol) in EtOH (180 mL) aq. NaOH (1M, 180 mL, 180 mmol) was added. The mixture was stirred at 80 °C for 8 h and then left at -5 °C overnight. The mixture was acidified to pH 1 with aq. 1M HCl and extracted with EtOAc (3x). The org. extracts were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue by FC ($MeOH/CH_2Cl_2$ 1:49 → 3:47 → 1:24 → 1:19 → 1:9 → 1:4) yielded the title compound, contaminated with (*rac.*)-(*1R**, *5S**)-7-[4-(2-hydroxyethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-7-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (7.09 g, 64%). R_f =0.40 $MeOH/CH_2Cl_2$ 1:9). R_t = 4.90; ES-: 589.16.

(*rac.*)-(*1R, *5S**)-7-[4-(3-Hydroxypropyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (V3)**

To a sol. of bicyclononene **H3** (13.50 g, 18.0 mmol) in EtOH (180 mL) aq. NaOH (1M, 180 mL, 180 mmol) was added. The mixture was heated to 40 °C and after 1 h to 80 °C. After 7 h, the mixture was left overnight at -5 °C. EtOH (100 mL) and aq. NaOH (1M, 50 mL, 50 mmol) were added and the sol. was heated to 80 °C for 6 h. After cooling to rt and adjustment of the pH to 1 with aq. 1M HCl, the mixture was extracted with EtOAc (3x). The combined org. extracts were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue by FC ($MeOH/CH_2Cl_2$ 1:49 → 3: 97 → 1:24 → 1:19 → 1:9 → 1:4) yielded the title compound (4.80 g, 55%). R_f = 0.50 ($MeOH/CH_2Cl_2$ 1:9). LC-MS: R_t = 4.99; ES-: 603.20.

Compounds of type W

(*rac.*)-(*1R, *5S**)-7-(4-Hydroxyphenyl)-6-(methylphenethylcarbamoyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (W1)**

To a susp. of bicyclononene **V1** (1.50 g, 2.66 mmol) in $CHCl_3$ (30 mL) was added methylphenethylamine (0.774 mL, 5.32 mmol). DMAP (32.5 mg, 0.266 mmol), HOBt (36 mg, 0.266 mmol), and EDC·HCl (765 mg, 3.99 mmol) were added successively. After 3 days at rt the mixture was diluted in CH_2Cl_2 and washed with aq. 1M HCl (1x) and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:9 → 1:4 → 3:7 → 2:3 → 1:1 → 3:2 → 7:3) yielded the title compound as a colorless solid (0.93 g, 51%). R_f = 0.25 (EtOAc/heptane 1:1). LC-MS: R_t = 5.86; ES-: 678.14.

(*rac.*)-(*1R, *5S**)-7-[4-(2-Hydroxyethyl)phenyl]-6-(methylphenethylcarbamoyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (W2)**

To a sol. of bicyclononene **V2** (7.09 g, 11.97 mmol) in $CHCl_3$ (140 mL) were added *N*-methylphenethylamine (3.48 mL, 24.0 mmol), DMAP (137 mg, 1.12 mmol), HOBt (151 mg, 1.12 mmol) and EDC·HCl (3.44 g, 18.0 mmol). The mixture was stirred at rt for 3 days, before it was diluted with CH_2Cl_2 and washed with aq. 1M HCl (1x) and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue purified by FC (MeOH/CH_2Cl_2 1:49 → 3:122 → 4:121 → 1:24 → 1:9 → 1:4) yielded the title compound (3.46 g, 41%). R_f = 0.26 (MeOH/CH_2Cl_2 1:19). LC-MS: R_t = 5.87; ES+: 708.40.

(*rac.*)-(*1R, *5S**)-7-[4-(3-Hydroxypropyl)phenyl]-6-(methylphenethylcarbamoyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (W3)**

To a sol. of bicyclononene **V3** (7.59 g, 12.5 mmol) in $CHCl_3$ (150 mL) were added methylphenethylamine (3.63 mL, 25.0 mmol), DMAP (153 mg, 1.25 mmol), HOBt (169 mg, 1.25 mmol) and EDC·HCl (3.80 g, 19.2 mmol). The mixture was stirred at rt for 3 days before it was diluted in CH_2Cl_2 and washed with aq. 1M HCl (1x) and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue by FC (MeOH/CH_2Cl_2 1:49 → 3:97 → 1:24 → 1:9 → 1:4) yielded the title compound (3.18 g, 35%). R_f = 0.42 (MeOH/CH_2Cl_2 1:19). LC-MS: R_t = 5.99; ES+: 744.50.

(*rac.*)-(*1R, *5S**)-3-Acetyl-6-hydroxymethyl-7-{4-[3-(2-methoxybenzyloxy)-propoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (X)**

To a sol. of bicyclononene **S1** (2.29 g, 3.21 mmol) in CH_2Cl_2 (100 mL) was added $BF_3 \cdot Et_2O$ (0.460 mL, 3.66 mmol) at -78 °C. The mixture was stirred at -78 °C for 30 min and DIBAL (1M in toluene, 6.42 mL, 6.42 mmol) was added. After 75 min, ice was added and the mixture was allowed to warm up to rt. CH_2Cl_2 was added and the mixture was washed with aq. 1M HCl (1x). The org. extracts were separated, dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:2 → 1:1 → EtOAc) yielded the title compound (1.01 g, 47%).

(*rac.*)-(*1R, *5S**)-3-Acetyl-6-formyl-7-{4-[3-(2-methoxybenzyloxy)propoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (Y)**

To a sol. of bicyclononene **X** (258 mg, 0.385 mmol) in CH_2Cl_2 (5 mL) was added to 0 °C Dess-Martin periodane (170 mg, 0.401 mmol) at 0 °C. After 45 min. at 0 °C a second portion periodane was added. The sol. was stirred for 15 min before the solvents were removed under reduced pressure. Direct purification of the residue by FC (EtOAc/heptane 2:3 → 1:1 → 3:2 → 7:3) yielded the title compound (188 mg, 73%). $R_f = 0.49$ (EtOAc). LC-MS: $R_t = 6.18$; ES+: 667.21.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-{4-[3-(2-methoxybenzyloxy)propoxy]phenyl}-6-methylaminomethyl-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (Z)**

To a sol. of bicyclononene **Y** (334 mg, 0.50 mmol) in MeOH (10 mL) methylamine (40% in water, 0.215 mL, 2.5 mmol) was added. The mixture was stirred at rt for 1 h and then cooled to 0 °C. $NaBH_4$ (20 mg, 0.50 mmol) was added. The mixture was stirred at rt for 4 h before K_2CO_3 (263 mg) was added. After evaporation under reduced pressure the residue was distributed between EtOAc and water. The org. extracts were separated, dried over $MgSO_4$, and filtered. The solvents were removed under reduced pressure. Purification of the

residue by RP18-MPLC yielded the title compound (130 mg, 38%). LC-MS: R_t = 1.00; ES+: 682.14.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Chlorophenoxy)propyl]phenyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AA)**

Bicyclononene **H6** (1.71 g, 2.3 mmol) was dissolved in EtOH (50 mL). Aq. 1M NaOH (50 mL) was added and the mixture was heated to 80 °C. The sol. was stirred for 5 h at 80 °C, then allowed to cool down to rt. After acidification to pH = 1-2 with aq. 1M HCl the mixture was extracted with EtOAc (3x). The combined org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 2:3 → 1:2 → 1:1) yielded the title compound (504 mg, 31 %). R_f = 0.30 (EtOAc/heptane 1:1). LC-MS: R_t = 6.21; ES-: 712.34.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Chlorophenoxy)propyl]phenyl}-6-{[2-(2-chlorophenyl)ethyl]methylcarbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AB)**

Bicyclononene **AA** (504 mg, 0.703 mmol) was dissolved in $CHCl_3$ (25 mL). [2-(2-chlorophenyl)ethyl]methylamine (Jaques B.; Wallace R. G., *Tetrahedron*, **1977**, *33*, 581; 238 mg, 1.40 mmol), DIPEA (0.240 mL, 1.40 mmol), DMAP (17 mg, 0.14 mmol), HOBt (19 mg, 0.10 mmol) and EDC·HCl (135 mg, 1.40 mmol) were added. The sol. was stirred at rt overnight. The mixture was diluted with CH_2Cl_2 and washed with water (1x). The org. extracts were dried over $MgSO_4$ and the solvents were removed under reduced pressure. Purification of the residue by filtration through silica gel yielded the title compound as a yellowish foam (336 mg, 55%).

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Chlorophenoxy)propyl]phenyl}-6-{[2-(2-chlorophenyl)ethyl]methylcarbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AC)**

Bicyclononene **AB** (336 mg, 0.378 mmol) was dissolved in CH_2Cl_2 (3 mL). 4M HCl/dioxane (13 mL) was added and the mixture was stirred at rt for 2 h. The solvents were removed under reduced pressure. Drying the residue at high vacuum yielded the title compound as a colorless foam that was used without further purification. LC-MS: R_t = 5.26; ES+: 765.85.

9-Methyl-7-oxo-3,9-diazabicyclo[3.3.1]nonane-3-carboxylic acid *tert*-butyl ester (AE)

(4-Benzyl-6-ethoxycarbonylmethyl-1-methylpiperazin-2-yl)acetic acid ethyl ester (Patent WO 92/05174) (71.0 g, 0.196 mol) was dissolved in MeOH (400 mL). TFA (77.8 mL, 1.02 mol) was added and the flask was purged with nitrogen. Pd/C (10%, 50% moisture, 3.6 g) was added. The flask was closed and purged with hydrogen (3x). After 1 day, the mixture was filtered through celite and washed with MeOH. The solvent was removed under reduced pressure and the foamy residue (92.7 g) was dried under high vacuum. A sol. of tBuOK (117.2 g, 1.04 mol) in toluene (3.07 L) was heated to reflux. A sol. of the crude piperazine formerly obtained, dissolved in THF (300 mL), was added dropwise over 50 min. The black mixture was stirred for 10 further min. and allowed to cool to rt. The mixture was cooled to 0 °C and AcOH (36.6 mL, 0.635 mol) was added. The solvents were removed under reduced pressure and the residue purified by FC ($MeOH/CH_2Cl_2$ 1:9 → 1:4 → 1:3). The fractions with an R_f-value close to 0.10 ($MeOH/CH_2Cl_2$ 1:9) were collected and the solvent removed under reduced pressure. The residue was dissolved in aq. 5M HCl (2 L) and the reaction mixture heated to reflux overnight. The mixture was allowed to cool to rt, then cooled to 0 °C with an ice bath. The pH was brought to 12 by adding carefully solid KOH. This mixture was extracted with CH_2Cl_2 (3x). The combined org. extracts were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The

residue was suspended in CH_2Cl_2 (400 mL) and cooled to 0 °C. DIPEA (19.1 mL, 112 mmol) was added. A sol. of Boc_2O (24.3 g, 113 mmol) in CH_2Cl_2 (200 mL) was added dropwise. The mixture was stirred for 1 h at 0 °C, then 1 h at rt. The mixture was washed with aq. 10% Na_2CO_3 (2x). The org. extracts were dried over $MgSO_4$, filtered and the solvents were evaporated under reduced pressure. The residue was purified by FC (EtOAc/heptane 1:1 → EtOAc). The title compound was obtained as a solid that could be recrystallized from heptane (15.6 g, 30%). R_f = 0.45 (MeOH/CH_2Cl_2 1:9). LC-MS: R_t = 1.55; ES+: 254.16.

(*1R*, *5S*)-9-Methyl-7-oxo-3,9-diazabicyclo[3.3.1]nonane-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-methyl ester (AF)

To a susp. of (-)-bis[(S)-1-phenylethyl]amine hydrochloride (226 mg, 0.864 mmol) in THF (3 mL) at 0 °C was added dropwise *n*-BuLi (1.6M in hexane, 1.136 mL, 1.808 mmol). The mixture was stirred for 1 h at 0 °C, then cooled to -78 °C. A sol. of bicyclononane **AE** (200 mg, 0.786 mmol) in THF (2 mL) was added dropwise over 3 min. The reaction mixture was stirred for 3 h at -78 °C, then methylcyanoformat (0.081 mL, 1.02 mmol) was added. The reaction mixture was stirred for 30 min. at -78 °C and a sol. of $AgNO_3$ (191 mg, 1.124 mmol) in H_2O/THF (1:1, 2 mL) was added. After 10 min., H_2O (1.5 mL) and AcOH (1.5 mL) were added and the reaction mixture was allowed to warm to rt. Ammoniac (25% in water) was added until the Ag-salt had completely dissolved. The reaction mixture was extracted with EtOAc (1x) and CH_2Cl_2 (2x). The combined org. extracts were dried over $MgSO_4$ and the solvents were removed under reduced pressure. Purification of the residue by FC (MeOH/CH_2Cl_2 1:14) yielded the title compound (167 mg, 68%). R_f = 0.37 (MeOH/CH_2Cl_2 1:9). LC-MS: R_t = 0.76; ES+: 313.10. ee = 82%.

(*1R*, *5S*)-9-Methyl-7-oxo-3,9-diazabicyclo[3.3.1]nonane-3,6-dicarboxylic acid 6-benzyl ester 3-*tert*-butyl ester (AG)

To a susp. of (-)-bis[(S)-1-phenylethyl]amine hydrochloride (226 mg, 0.864 mmol) in THF (3 mL) at 0 °C was added dropwise *n*-BuLi (1.6M in hexane, 1.136 mL, 1.808 mmol). The mixture was stirred for 1 h at 0 °C, then cooled to -78 °C. A sol. of bicyclononane **AE** (200 mg, 0.786 mmol) in THF (2 mL) was added dropwise over 3 min. The reaction mixture was stirred for 3 h at -78 °C, then methylcyanoformat (0.081 mL, 1.02 mmol) was added. The reaction mixture was stirred for 30 min. at -78 °C and a sol. of $AgNO_3$ (191 mg, 1.124 mmol) in H_2O/THF (1:1, 2 mL) was added. After 10 min., H_2O (1.5 mL) and AcOH (1.5 mL) were added and the reaction mixture was allowed to warm to rt. Ammoniac (25% in water) was added until the Ag-salt had completely dissolved. The reaction mixture was extracted with EtOAc (1x) and CH_2Cl_2 (2x). The combined org. extracts were dried over $MgSO_4$ and the solvents were removed under reduced pressure. Purification of the residue by FC (MeOH/CH_2Cl_2 1:14) yielded the title compound (150 mg, 49%). R_f = 0.50 (MeOH/CH_2Cl_2 1:9). LC-MS: R_t = 0.87; ES+: 389.09. ee = 84%.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-{4-[2-(2-bromo-5-fluorophenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AH)**

A sol. of bicyclononene **S3** (900 mg, 1.60 mmol) in toluene (15 mL) was purged with N_2 (4x). 2-Bromo-5-fluorophenol (0.267 mL, 2.4 mmol), TMAD (344 mg, 2.00 mmol) and tributylphosphine (1.18 mL, 4.80 mmol) were added and the reaction mixture was heated to reflux for 1 h. The mixture was allowed to cool to rt, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:24 → 1:9 → 2:3 → 7:3) yielded the title compound (1.06 g, 90%). R_f = 0.58 (EtOAc). LC-MS: R_t = 6.52; ES+: 733.00.

Compounds of type AJ

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-{4-[2-(2-bromo-5-fluorophenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AJ1)**

A mixture of bicyclononene **AH** (1.06 g, 1.44 mmol) in EtOH (30 mL) and aq. 1M NaOH (30 mL) was stirred efficiently at 80 °C for 2.5 h. The mixture was allowed to cool to rt, acidified with aq. 1M HCl, and extracted with EtOAc (3x). The combined org. phases were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:1 → 3:1 → EtOAc → MeOH/EtOAc 1:19 → 1:9) yielded the title compound (845 mg, 83%). R_f = 0.10 (EtOAc). LC-MS: R_t = 5.78; ES-: 702.81.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AJ2)**

A sol. of bicyclononene **AR1** (296 mg, 0.39 mmol) in MeOH (10 mL) at 0 °C was purged with N_2 (3x). Pd/C (10%, cat. amount) was added and the mixture was purged with H_2 (4x). The mixture was stirred under H_2 for 2 h at 0 °C, and was filtered through *Celite*. The solvents were removed under reduced pressure and the residue was dried under high vacuum (200 mg, 80%). It was used without further purification. LC-MS: R_t = 5.83.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-{4-[3-(3-fluorophenoxy)propyl]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (AJ3)**

As for compound **AJ2**, but from **AR2** (205 mg, 0.25 mmol), Pd/C (cat. amount) and MeOH (10 mL). The crude material (100 mg, 56%) was used without further purification. LC-MS: R_t = 5.81.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AJ4)**

As for compound **AJ1**, but from bicyclononene **BL** (1.55 g, 2.07 mmol), EtOH (55 mL) and aq. 1M NaOH (55 mL). Purification of the residue by FC (EtOAc/heptane 1:1 → EtOAc → MeOH/EtOAc 1:9) yielded the title compound (1.17 g, 78%). R_f = 0.20 (EtOAc). R_t = 6.02; ES+: 721.12.

Compounds of type AK

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Bromo-5-fluorophenoxy)ethyl]phenyl}-6-(methyl-phenethylcarbamoyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK1)**

A sol. of bicyclononene **W2** (1.68 g, 2.37 mmol) in toluene (50 mL) was purged with N_2 (4x). 2-Bromo-5-fluorophenol (0.403 mL, 3.56 mmol), azodicarboxylic dipiperidide (897 mg, 3.56 mmol) and tributyl phosphine (1.62 mL, 7.12 mmol) were added. The mixture was heated to reflux for 2 h. The mixture was then allowed to cool to rt and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:19 → 1:9 → 1:4 → 1:1 → 3:1) yielded the title compound (1.88 g, 90%). R_f = 0.80 (EtOAc). LC-MS: R_t = 7.30.

(*rac.*)-(*1R, *5S**)-6-[(2-Chlorobenzyl)cyclopropylcarbamoyl]-7-{4-[3-(2,3,6-tri-fluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarbo-xylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK2)**

A mixture of bicyclononene **AY1** (12.15 g, 16 mmol), (2-chlorobenzyl)-cyclopropylamine (9.08 g, 50 mmol), DIPEA (10.9 mL, 64 mmol), DMAP (488 mg, 4 mmol), HOBt (2.43 g, 18 mmol) and EDC·HCl (4.60 g, 24 mmol) in

CH_2Cl_2 (250 mL) was stirred overnight. The mixture was diluted with CH_2Cl_2, and washed with aq. 1M HCl (3x) and with aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:5 → 1:3 → 1:2) yielded the title compound (9.10 g, 63%). LC-MS: R_t = 7.68.

(*rac.*)-(*1R, *5S**)-6-(Benzylcyclopropylcarbamoyl)-7-{4-[3-(2,3,6-trifluoro-phenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK3)**

As for bicyclononene **AK2**, but from bicyclononene **AY1** (552 mg, 0.75 mmol), benzylcyclopropylamine (Loeppky, R. N.; *et al.*, *J. Org. Chem.*, **2000**, *65*, 96; 221 mg, 1.50 mmol), DIPEA (0.515 mL, 3.00 mmol), DMAP (23 mg, 0.19 mmol), HOBt (101 mg, 0.75 mmol) and EDC·HCl (216 mg, 1.12 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (570 mg, 88%). LC-MS: R_t = 1.28.

(*rac.*)-(*1R, *5S**)-6-[(2-chlorobenzyl)ethylcarbamoyl]-7-{4-[3-(2,3,6-trifluoro-phenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK4)**

As for bicyclononene **AK2**, but from bicyclononene **AY1** (552 mg, 0.75 mmol), (2-chlorobenzyl)ethylamine (Ishihara, Y; *et al.*; *Chem. Pharm. Bull.*, **1991**, *39*, 3225; 255 mg, 1.50 mmol), DIPEA (0.515 mL, 3.00 mmol), DMAP (23 mg, 0.19 mmol), HOBt (101 mg, 0.75 mmol) and EDC·HCl (216 mg, 1.12 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (543 mg, 82%). LC-MS: R_t = 1.29.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(2-fluorobenzyl)carbamoyl]-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK5)**

As for bicyclononene **AK2**, but from bicyclononene **AY1** (552 mg, 0.75 mmol), cyclopropyl-(2-fluorobenzyl)amine (248 mg, 1.50 mmol), DIPEA (0.515 mL, 3.00 mmol), DMAP (23 mg, 0.19 mmol), HOBt (101 mg, 0.75 mmol) and EDC·HCl (216 mg, 1.12 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (526 mg, 79%). LC-MS: $R_t = 1.28$.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(3-trifluoromethylbenzyl)carbamoyl]-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK6)**

As for bicyclononene **AK2**, but from bicyclononene **AY1** (552 mg, 0.75 mmol), cyclopropyl-(3-trifluoromethyl-benzyl)amine (Brabander, H. J.; *et al.*; *J. Org. Chem.*, **1967**, *32*, 4053; 323 mg, 1.50 mmol), DIPEA (0.515 mL, 3.00 mmol), DMAP (23 mg, 0.19 mmol), HOBt (101 mg, 0.75 mmol) and EDC·HCl (216 mg, 1.12 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (551 mg, 79%). LC-MS: $R_t = 1.25$.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(2-methylbenzyl)carbamoyl]-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK7)**

As for bicyclononene **AK2**, but from bicyclononene **AY1** (552 mg, 0.75 mmol), cyclopropyl-(2-methylbenzyl)-amine (242 mg, 1.50 mmol), DIPEA (0.515 mL, 3.00 mmol), DMAP (23 mg, 0.19 mmol), HOBt (101 mg, 0.75 mmol) and EDC·HCl (216 mg, 1.12 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (553 mg, 84%). LC-MS: $R_t = 1.29$.

(*rac.*)-(*1R, *5S**)-6-{Cyclopropyl-[2-(4-methoxyphenoxy)ethyl]carbamoyl}-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-**

ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (AK8)

As for bicyclononene **AK2**, but from bicyclononene **AY1** (552 mg, 0.75 mmol), cyclopropyl-[2-(4-methoxy-phenoxy)ethyl]amine (311 mg, 1.50 mmol), DIPEA (0.515 mL, 3.00 mmol), DMAP (23 mg, 0.19 mmol), HOBt (101 mg, 0.75 mmol) and EDC·HCl (216 mg, 1.12 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (566 mg, 82%). LC-MS: $R_t = 1.28$.

(*rac.*)-(*1R, *5S**)-6-{Cyclopropyl-[2-(2-methoxyphenoxy)ethyl]carbamoyl}-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (AK9)**

As for bicyclononene **AK2**, but from bicyclononene **AY1** (552 mg, 0.75 mmol), cyclopropyl-[2-(2-methoxy-phenoxy)ethyl]amine (311 mg, 1.50 mmol), DIPEA (0.515 mL, 3.00 mmol), DMAP (23 mg, 0.19 mmol), HOBt (101 mg, 0.75 mmol) and EDC·HCl (216 mg, 1.12 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (570 mg, 82%). LC-MS: $R_t = 1.28$.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(2-*m*-tolyloxyethyl)carbamoyl]-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK10)**

As for bicyclononene **AK2**, but from bicyclononene **AY1** (552 mg, 0.75 mmol), cyclopropyl-(2-*m*-tolyloxy-ethyl)amine (287 mg, 1.50 mmol), DIPEA (0.515 mL, 3.00 mmol), DMAP (23 mg, 0.19 mmol), HOBt (101 mg, 0.75 mmol) and EDC·HCl (216 mg, 1.12 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (506 mg, 74%). LC-MS: $R_t = 1.30$.

(*rac.*)-(*1R, *5S**)-6-{Cyclopropyl-[2-(3,4-dimethylphenoxy)ethyl]carbamoyl}-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK11)**

As for bicyclononene **AK2**, but from bicyclononene **AY1** (552 mg, 0.75 mmol), cyclopropyl-[2-(3,4-dimethyl-phenoxy)ethyl]amine (462 mg, 1.50 mmol), DIPEA (0.515 mL, 3.00 mmol), DMAP (23 mg, 0.19 mmol), HOBt (101 mg, 0.75 mmol) and EDC·HCl (216 mg, 1.12 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (693 mg, 100%). LC-MS: $R_t = 1.28$.

(*rac.*)-(*1R, *5S**)-6-(Cyclopropylphenethylcarbamoyl)-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK12)**

As for bicyclononene **AK2**, but from bicyclononene **AY1** (552 mg, 0.75 mmol), cyclopropylphenethylamine (Smith, P. W.; *et al.*; *J. Med. Chem.*, **1998**, *41*, 787; 242 mg, 1.50 mmol), DIPEA (0.515 mL, 3.00 mmol), DMAP (23 mg, 0.19 mmol), HOBt (101 mg, 0.75 mmol) and EDC·HCl (216 mg, 1.12 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (510 mg, 77%). LC-MS: $R_t = 1.28$.

(*rac.*)-(*1R, *5S**)-6-{[2-(2-Chlorophenyl)ethyl]cyclopropylcarbamoyl}-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK13)**

As for bicyclononene **AK2**, but from bicyclononene **AY1** (552 mg, 0.75 mmol), [2-(2-chlorophenyl)ethyl]-cyclopropylamine (294 mg, 1.50 mmol), DIPEA (0.515 mL, 3.00 mmol), DMAP (23 mg, 0.19 mmol), HOBt (101 mg, 0.75 mmol) and EDC·HCl (216 mg, 1.12 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (540 mg, 79%). LC-MS: $R_t = 1.28$.

(*rac.*)-(*1R, *5S**)-6-{Cyclopropyl-[2-(2,3-difluorophenyl)ethyl]carbamoyl}-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK14)**

As for bicyclononene **AK2**, but from bicyclononene **AY1** (552 mg, 0.75 mmol), cyclopropyl-[2-(2,3-difluoro-phenyl)ethyl]amine (296 mg, 1.50 mmol), DIPEA (0.515 mL, 3.00 mmol), DMAP (23 mg, 0.19 mmol), HOBt (101 mg, 0.75 mmol) and EDC·HCl (216 mg, 1.12 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (572 mg, 83%). LC-MS: R_t = 1.28.

(*rac.*)-(*1R, *5S**)-6-{Cyclopropyl-[2-(4-fluorophenyl)ethyl]carbamoyl}-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK15)**

As for bicyclononene **AK2**, but from bicyclononene **AY1** (552 mg, 0.75 mmol), cyclopropyl-[2-(4-fluoro-phenyl)ethyl]amine (269 mg, 1.50 mmol), DIPEA (0.515 mL, 3.00 mmol), DMAP (23 mg, 0.19 mmol), HOBt (101 mg, 0.75 mmol) and EDC·HCl (216 mg, 1.12 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (533 mg, 79%). LC-MS: R_t = 1.28.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(2-*o*-tolylethyl)carbamoyl]-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK16)**

As for bicyclononene **AK2**, but from bicyclononene **AY1** (552 mg, 0.75 mmol), cyclopropyl-(2-*o*-tolylethyl)-amine (263 mg, 1.50 mmol), DIPEA (0.515 mL, 3.00 mmol), DMAP (23 mg, 0.19 mmol), HOBt (101 mg, 0.75 mmol) and EDC·HCl

(216 mg, 1.12 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (562 mg, 84%). LC-MS: R_t = 1.29.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(3,5-dimethoxybenzyl)carbamoyl]-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK17)**

As for bicyclononene **AK2**, but from bicyclononene **AY1** (552 mg, 0.75 mmol), cyclopropyl-(3,5-dimethoxy-benzyl)amine (311 mg, 1.50 mmol), DIPEA (0.515 mL, 3.00 mmol), DMAP (23 mg, 0.19 mmol), HOBt (101 mg, 0.75 mmol) and EDC·HCl (216 mg, 1.12 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (530 mg, 76%). LC-MS: R_t = 1.28.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(2-*p*-tolylethyl)carbamoyl]-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK18)**

As for bicyclononene **AK2**, but from bicyclononene **AY1** (552 mg, 0.75 mmol), cyclopropyl-(2-*p*-tolylethyl)-amine (263 mg, 1.50 mmol), DIPEA (0.515 mL, 3.00 mmol), DMAP (23 mg, 0.19 mmol), HOBt (101 mg, 0.75 mmol) and EDC·HCl (216 mg, 1.12 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (530 mg, 79%). LC-MS: R_t = 1.30.

(*rac.*)-(*1R, *5S**)-6-{Cyclopropyl-[2-(2-hydroxyethyl)benzyl]carbamoyl}-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK19)**

As for bicyclononene **AK2**, but from bicyclononene **AY1** (1.30, 1.77 mmol), (2-allylbenzyl)cyclopropyl-amine (992 mg, 5.30 mmol), DIPEA (1.01 mL, 7.08

mmol), DMAP (54 mg, 0.44 mmol), HOBt (263 mg, 1.95 mmol) and EDC·HCl (509 mg, 2.66 mmol) in CH_2Cl_2 (25 mL). Purification by FC yielded the intermediate compound (1.49 g, 93%). LC-MS: R_t = 7.81.

Then as for compound **AT**, but from the former intermediate compound (1.49 g, 1.65 mmol), NMO·H_2O (245 mg, 1.82 mmol), and OsO_4 (2.5% in *tert*-BuOH, 0.207 mL, 0.017 mmol) in THF (4 mL), *tert*-BuOH (2 mL) and water (1 mL). Purification of the residue by FC (EtOAc/heptane 1:4 → 2:3 → 3:2 → 4:1 → EtOAc) yielded the 2nd intermediate compound (866 mg, 56%). R_f = 0.50 (EtOAc). LC-MS: R_t = 6.95.

Then as for compound **AU**, but from the 2nd intermediate compound (866 mg, 0.922 mmol) and $NaIO_4$ (217 mg, 1.01 mmol) in THF (8 mL) and water (2 mL). Purification of the residue by FC (EtOAc/heptane 1:4 → 2:3) yielded the 3rd intermediate compound (751 mg, 90%). R_f = 0.75 (EtOAc).

Finally as for compound **AV**, but from the 3rd intermediate compound (751 mg, 0.828 mmol) and $NaBH_4$ (35 mg, 0.9 mmol) in MeOH (10 mL). Purification of the residue by FC (EtOAc/heptane 2:3) yielded the title compound (599 mg, 80%). LC-MS: R_t = 7.30.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-[(2-chlorobenzyl)cyclopropylcarbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK20)**

As for bicyclononene **AK2**, but from bicyclononene **AY2** (7.68 g, 9.86 mmol), (2-chlorobenzyl)cyclopropylamine (5.37, 29.6 mmol), DIPEA (6.75 mL, 39.4 mmol), DMAP (301 mg, 2.47 mmol), HOBt (1.46 mg, 10.8 mmol) and EDC·HCl (2.84 g, 14.8 mmol) in CH_2Cl_2 (150 mL). Purification by FC (EtOAc/heptane 1:4 → 3:7 → 2:3 → 1:1) yielded the title compound (3.7 g, 40%). R_f = 0.55 (EtOAc/heptane 1:1). LC-MS: R_t = 7.97.

(*rac.*)-(*1R, *5S**)-6-(Benzylcyclopropylcarbamoyl)-7-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK21)**

As for bicyclononene **AK2**, but from bicyclononene **AY2** (779 mg, 1.00 mmol), benzylcyclopropylamine (Loeppky, R. N.; *et al.*, *J. Org. Chem.*, **2000**, *65*, 96; 1.27 g, 1.50 mmol), DIPEA (0.684 mL, 4.00 mmol), DMAP (30 mg, 0.25 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (287 mg, 1.50 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (520 mg, 57%). LC-MS: R_t = 7.79.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-[(2-chlorobenzyl)ethylcarbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK22)**

As for bicyclononene **AK2**, but from bicyclononene **AY2** (779 mg, 1.00 mmol), (2-chlorobenzyl)ethylamine (Ishihara, Y; *et al.*; *Chem. Pharm. Bull.*, **1991**, *39*, 3225; 254 mg, 1.50 mmol), DIPEA (0.684 mL, 4.00 mmol), DMAP (30 mg, 0.25 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (287 mg, 1.50 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (475 mg, 51%). LC-MS: R_t = 7.82.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-[cyclopropyl-(2-fluorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK23)**

As for bicyclononene **AK2**, but from bicyclononene **AY2** (779 mg, 1.00 mmol), cyclopropyl-(2-fluorobenzyl)amine (247 mg, 1.50 mmol), DIPEA (0.684 mL, 4.00 mmol), DMAP (30 mg, 0.25 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (287 mg, 1.50 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (465 mg, 50%). LC-MS: R_t = 7.69.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-[cyclopropyl-(3-trifluoromethylbenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK24)**

As for bicyclononene **AK2**, but from bicyclononene **AY2** (779 mg, 1.00 mmol), cyclopropyl-(3-trifluoromethylbenzyl)amine (Brabander, H. J.; *et al.*; *J. Org. Chem.*, **1967**, *32*, 4053; 323 mg, 1.50 mmol), DIPEA (0.684 mL, 4.00 mmol), DMAP (30 mg, 0.25 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (287 mg, 1.50 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (345 mg, 35%). LC-MS: $R_t = 7.76$.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-[cyclopropyl-(2-methylbenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK25)**

As for bicyclononene **AK2**, but from bicyclononene **AY2** (779 mg, 1.00 mmol), cyclopropyl-(2-methylbenzyl)amine (242 mg, 1.50 mmol), DIPEA (0.684 mL, 4.00 mmol), DMAP (30 mg, 0.25 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (287 mg, 1.50 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (722 mg, 78%). LC-MS: $R_t = 7.77$.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-{cyclopropyl-[2-(4-methoxyphenoxy)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK26)**

As for bicyclononene **AK2**, but from bicyclononene **AY2** (779 mg, 1.00 mmol), cyclopropyl-(4-methoxyphenoxymethyl)amine (311 mg, 1.50 mmol), DIPEA (0.684 mL, 4.00 mmol), DMAP (30 mg, 0.25 mmol), HOBt (135 mg, 1.00 mmol)

and EDC·HCl (287 mg, 1.50 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (579 mg, 60%). LC-MS: R_t = 7.64.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-[cyclopropyl-(2-*m*-tolyloxyethyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK27)**

As for bicyclononene **AK2**, but from bicyclononene **AY2** (779 mg, 1.00 mmol), cyclopropyl-*m*-tolyloxymethylamine (311 mg, 1.50 mmol), DIPEA (0.684 mL, 4.00 mmol), DMAP (30 mg, 0.25 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (287 mg, 1.50 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (340 mg, 36%). LC-MS: R_t = 7.83.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-{cyclopropyl-[2-(3,4-dimethylphenoxy)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]-non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK28)**

As for bicyclononene **AK2**, but from bicyclononene **AY2** (779 mg, 1.00 mmol), cyclopropyl-(3,4-dimethylphenoxymethyl)amine (308 mg, 1.50 mmol), DIPEA (0.684 mL, 4.00 mmol), DMAP (30 mg, 0.25 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (287 mg, 1.50 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (470 mg, 49%). LC-MS: R_t = 7.93.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-(cyclopropylphenethylcarbamoyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK29)**

As for bicyclononene **AK2**, but from bicyclononene **AY2** (779 mg, 1.00 mmol), cyclopropyl-phenethylamine (Smith, P. W.; *et al.*; *J. Med. Chem.*, **1998**, *41*, 787; 242 mg, 1.50 mmol), DIPEA (0.684 mL, 4.00 mmol), DMAP (30 mg, 0.25

mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (287 mg, 1.50 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (449 mg, 49%). LC-MS: $R_t = 7.72$.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-{[2-(2-chlorophenyl)ethyl]cyclopropylcarbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK30)**

As for bicyclononene **AK2**, but from bicyclononene **AY2** (779 mg, 1.00 mmol), [2-(2-chloro-phenyl)ethyl]cyclopropylamine (294 mg, 1.50 mmol), DIPEA (0.684 mL, 4.00 mmol), DMAP (30 mg, 0.25 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (287 mg, 1.50 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (605 mg, 63%). LC-MS: $R_t = 7.89$.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-{cyclopropyl-[2-(2,3-difluorophenyl)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (AK31)**

As for bicyclononene **AK2**, but from bicyclononene **AY2** (779 mg, 1.00 mmol), cyclopropyl-[2-(2,3-difluorophenyl)ethyl]amine (296 mg, 1.50 mmol), DIPEA (0.684 mL, 4.00 mmol), DMAP (30 mg, 0.25 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (287 mg, 1.50 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (670 mg, 70%). LC-MS: $R_t = 7.70$.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-{cyclopropyl-[2-(4-fluorophenyl)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (AK32)**

As for bicyclononene **AK2**, but from bicyclononene **AY2** (779 mg, 1.00 mmol), cyclopropyl-[2-(4-fluorophenyl)ethyl]amine (269 mg, 1.50 mmol), DIPEA (0.684 mL, 4.00 mmol), DMAP (30 mg, 0.25 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (287 mg, 1.50 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (638 mg, 68%). LC-MS: $R_t = 7.70$.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-[cyclopropyl-(2-*o*-tolylethyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK33)**

As for bicyclononene **AK2**, but from bicyclononene **AY2** (779 mg, 1.00 mmol), cyclopropyl-(2-*o*-tolylethyl)amine (263 mg, 1.50 mmol), DIPEA (0.684 mL, 4.00 mmol), DMAP (30 mg, 0.25 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (287 mg, 1.50 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (659 mg, 70%). LC-MS: $R_t = 7.58$.

1:1 Mixture of (*rac.*)-(*1R, *5S**)-7-{4-[3-(2-bromo-5-fluorophenoxy)propyl]-phenyl}-6-[((*2R**)-2-hydroxy-2-phenylethyl)methylcarbamoyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester and (*rac.*)-(*1R**, *5S**)-7-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-6-[((*2S**)-2-hydroxy-2-phenylethyl)methyl-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK34)**

As for bicyclononene **AK2**, but from bicyclononene **AY2** (779 mg, 1.00 mmol), (*rac.*)-2-methylamino-1-phenylethanol (310 mg, 1.50 mmol), DIPEA (0.684 mL, 4.00 mmol), DMAP (30 mg, 0.25 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (287 mg, 1.50 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compounds (456 mg, 50%). LC-MS: $R_t = 7.42$.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-[cyclopropyl-(3,5-dimethoxybenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (AK35)**

As for bicyclononene **AK2**, but from bicyclononene **AY2** (779 mg, 1.00 mmol), cyclopropyl-(3,5-dimethoxybenzyl)amine (311 mg, 1.50 mmol), DIPEA (0.684 mL, 4.00 mmol), DMAP (30 mg, 0.25 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (287 mg, 1.50 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (736 mg, 76%). LC-MS: R_t = 7.73.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-[cyclopropyl-(2-*p*-tolylethyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK36)**

As for bicyclononene **AK2**, but from bicyclononene **AY2** (779 mg, 1.00 mmol), cyclopropyl-(2-*p*-tolylethyl)amine (263 mg, 1.50 mmol), DIPEA (0.684 mL, 4.00 mmol), DMAP (30 mg, 0.25 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (287 mg, 1.50 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (718 mg, 77%). LC-MS: R_t = 7.73.

(*rac.*)-(*1R, *5S**)-6-[(2-Allylbenzyl)cyclopropylcarbamoyl]-7-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarbo-xylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK37)**

As for bicyclononene **AK2**, but from bicyclononene **AY2** (1.45, 2.00 mmol), (2-allylbenzyl)cyclopropylamine (1.12 g, 6.00 mmol), DIPEA (1.37 mL, 8.00 mmol), DMAP (62 mg, 0.50 mmol), HOBt (298 mg, 2.20 mmol) and EDC·HCl (576 mg, 3.00 mmol) in CH_2Cl_2 (20 mL). Purification by FC yielded the intermediate compound (1.77 g, 93%). LC-MS: R_t = 7.95.

Then as for compound **AT**, but from the former intermediate compound (1.77 g, 1.86 mmol), NMO·H_2O (516 mg, 3.82 mmol), and OsO_4 (2.5% in *tert*-BuOH, 0.276 mL, 0.023 mmol) in THF (40 mL), *tert*-BuOH (20 mL) and water (10 mL). Purification of the residue by FC (EtOAc/heptane 1:4 → 2:3 → 3:2 → 4:1 → EtOAc) yielded the 2nd intermediate compound (548 mg, 27%). R_f = 0.60 (EtOAc). LC-MS: R_t = 7.43; ES+: 980.18.

Then as for compound **AU**, but from the 2nd intermediate compound (928 mg, 0.945 mmol) and $NaIO_4$ (222 mg, 1.04 mmol) in THF (8 mL) and water (2 mL). Purification of the residue by FC (EtOAc/heptane 1:4 → 2:3) yielded the 3rd intermediate compound (868 mg, 97%). R_f = 0.80 (EtOAc).

Finally as for compound **AV**, but from the 3rd intermediate compound (868 mg, 0.914 mmol) and $NaBH_4$ (38 mg, 1.0 mmol) in MeOH (10 mL). Purification of the residue by FC (EtOAc/heptane 2:3) yielded the title compound (603 mg, 69%). LC-MS: R_t = 7.44.

(*rac.*)-(*1R, *5S**)-6-[(2-Chlorbenzyl)cyclopropylcarbamoyl]-7-{4-[2-(2,3,5-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK38)**

As for bicyclononene **AK2**, but from bicyclononene **AY3** (411 mg, 0.58 mmol), (2-chlorobenzyl)-cyclopropylamine (211 mg, 1.16 mmol), DIPEA (0.397 mL, 2.32 mmol), DMAP (18 mg, 0.15 mmol), HOBt (86 mg, 0.64 mmol) and EDC·HCl (167 mg, 0.87 mmol) in CH_2Cl_2 (8 mL). Purification by FC yielded the title compound (312 mg, 62%). LC-MS: R_t = 7.66.

(*rac.*)-(*1R, *5S**)-6-(Benzylcyclopropylcarbamoyl)-7-{4-[2-(2,3,5-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK39)**

As for bicyclononene **AK2**, but from bicyclononene **AY3** (411 mg, 0.58 mmol), benzyl-cyclopropylamine (Loeppky, R. N.; *et al.*, *J. Org. Chem.*, **2000**, *65*, 96;

171 mg, 1.16 mmol), DIPEA (0.397 mL, 2.32 mmol), DMAP (18 mg, 0.15 mmol), HOBt (86 mg, 0.64 mmol) and EDC·HCl (167 mg, 0.87 mmol) in CH_2Cl_2 (8 mL). Purification by FC yielded the title compound (340 mg, 70%). LC-MS: $R_t = 8.12$.

(*rac.*)-(*1R, *5S**)-6-[(2-Chlorobenzyl)ethylcarbamoyl]-7-{4-[2-(2,3,5-trimethyl-phenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK40)**

As for bicyclononene **AK2**, but from bicyclononene **AY3** (411 mg, 0.58 mmol), (2-chlorobenzyl)-ethylamine (Ishihara, Y; *et al.*; *Chem. Pharm. Bull.*, **1991**, *39*, 3225; 197 mg, 1.16 mmol), DIPEA (0.397 mL, 2.32 mmol), DMAP (18 mg, 0.15 mmol), HOBt (86 mg, 0.64 mmol) and EDC·HCl (167 mg, 0.87 mmol) in CH_2Cl_2 (8 mL). Purification by FC yielded the title compound (374 mg, 74%). LC-MS: $R_t = 8.30$.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(2-fluorobenzyl)carbamoyl]-7-{4-[2-(2,3,5-tri-methylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9dicarboxy-lic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK41)**

As for bicyclononene **AK2**, but from bicyclononene **AY3** (411 mg, 0.58 mmol), cyclopropyl-(2-fluorobenzyl)amine (192 mg, 1.16 mmol), DIPEA (0.397 mL, 2.32 mmol), DMAP (18 mg, 0.15 mmol), HOBt (86 mg, 0.64 mmol) and EDC·HCl (167 mg, 0.87 mmol) in CH_2Cl_2 (8 mL). Purification by FC yielded the title compound (350 mg, 70%). LC-MS: $R_t = 8.13$.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(3-trifluoromethylbenzyl)carbamoyl]-7-{4-[2-(2,3,5-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK42)**

As for bicyclononene **AK2**, but from bicyclononene **AY3** (411 mg, 0.58 mmol), cyclopropyl-(3-trifluoromethylbenzyl)amine (Brabander, H. J.; *et al.*; *J. Org. Chem.*, **1967**, *32*, 4053; 250 mg, 1.16 mmol), DIPEA (0.397 mL, 2.32 mmol), DMAP (18 mg, 0.15 mmol), HOBt (86 mg, 0.64 mmol) and EDC·HCl (167 mg, 0.87 mmol) in CH_2Cl_2 (8 mL). Purification by FC yielded the title compound (294 mg, 56%). LC-MS: $R_t = 8.16$.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(2-methylbenzyl)carbamoyl]-7-{4-[2-(2,3,5-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK43)**

As for bicyclononene **AK2**, but from bicyclononene **AY3** (411 mg, 0.58 mmol), cyclopropyl-(2-methylbenzyl)amine (187 mg, 1.16 mmol), DIPEA (0.397 mL, 2.32 mmol), DMAP (18 mg, 0.15 mmol), HOBt (86 mg, 0.64 mmol) and EDC·HCl (167 mg, 0.87 mmol) in CH_2Cl_2 (8 mL). Purification by FC yielded the title compound (294 mg, 56%). LC-MS: $R_t = 8.15$.

(*rac.*)-(*1R, *5S**)-6-{Cyclopropyl-[2-(4-methoxyphenoxy)ethyl]carbamoyl}-7-{4-[2-(2,3,5-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK44)**

As for bicyclononene **AK2**, but from bicyclononene **AY3** (411 mg, 0.58 mmol), cyclopropyl-[2-(4-methoxyphenoxy)ethyl]amine (187 mg, 1.16 mmol), DIPEA (0.397 mL, 2.32 mmol), DMAP (18 mg, 0.15 mmol), HOBt (86 mg, 0.64 mmol) and EDC·HCl (167 mg, 0.87 mmol) in CH_2Cl_2 (8 mL). Purification by FC yielded the title compound (159 mg, 30%). LC-MS: $R_t = 7.93$.

(*rac.*)-(*1R, *5S**)-6-{Cyclopropyl-[2-(3-methoxyphenoxy)ethyl]carbamoyl}-7-{4-[2-(2,3,5-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-

ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (AK45)

As for bicyclononene **AK2**, but from bicyclononene **AY3** (411 mg, 0.58 mmol), cyclopropyl-[2-(3-methoxyphenoxy)ethyl]amine (287 mg, 1.16 mmol), DIPEA (0.397 mL, 2.32 mmol), DMAP (18 mg, 0.15 mmol), HOBt (86 mg, 0.64 mmol) and EDC·HCl (167 mg, 0.87 mmol) in CH_2Cl_2 (8 mL). Purification by FC yielded the title compound (237 mg, 45%). LC-MS: $R_t = 7.69$.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(2-*m*-tolyloxyethyl)carbamoyl]-7-{4-[2-(2,3,5-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicar-boxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK46)**

As for bicyclononene **AK2**, but from bicyclononene **AY3** (411 mg, 0.58 mmol), cyclopropyl-(2-*m*-tolyloxyethyl)amine (222 mg, 1.16 mmol), DIPEA (0.397 mL, 2.32 mmol), DMAP (18 mg, 0.15 mmol), HOBt (86 mg, 0.64 mmol) and EDC·HCl (167 mg, 0.87 mmol) in CH_2Cl_2 (8 mL). Purification by FC yielded the title compound (185 mg, 36%). LC-MS: $R_t = 8.12$.

(*rac.*)-(*1R, *5S**)-6-(Cyclopropylphenethylcarbamoyl)-7-{4-[2-(2,3,6-trimethyl-phenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK47)**

As for bicyclononene **AK2**, but from bicyclononene **AY3** (590 mg, 0.83 mmol), cyclopropyl-phenethylamine (Smith, P. W.; *et al.*; *J. Med. Chem.*, **1998**, *41*, 787; 402 mg, 2.49 mmol), DIPEA (0.568 mL, 3.32 mmol), DMAP (25 mg, 0.21 mmol), HOBt (169 mg, 1.25 mmol) and EDC·HCl (239 mg, 1.25 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (309 mg, 44%). LC-MS: $R_t = 8.01$.

(*rac.*)-(*1R, *5S**)-6-{[2-(2-Chlorophenyl)ethyl]cyclopropylcarbamoyl}-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK48)**

As for bicyclononene **AK2**, but from bicyclononene **AY3** (590 mg, 0.83 mmol), [2-(2-chloro-phenyl)ethyl]cyclopropylamine (487 mg, 2.49 mmol), DIPEA (0.568 mL, 3.32 mmol), DMAP (25 mg, 0.21 mmol), HOBt (169 mg, 1.25 mmol) and EDC·HCl (239 mg, 1.25 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (272 mg, 37%). LC-MS: $R_t = 8.20$.

(*rac.*)-(*1R, *5S**)-6-{Cyclopropyl-[2-(2,3-difluorophenyl)ethyl]carbamoyl}-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK49)**

As for bicyclononene **AK2**, but from bicyclononene **AY3** (590 mg, 0.83 mmol), cyclopropyl-[2-(2,3-difluorophenyl)ethyl]amine (491 mg, 2.49 mmol), DIPEA (0.568 mL, 3.32 mmol), DMAP (25 mg, 0.21 mmol), HOBt (169 mg, 1.25 mmol) and EDC·HCl (239 mg, 1.25 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (309 mg, 42%). LC-MS: $R_t = 7.98$.

(*rac.*)-(*1R, *5S**)-6-{Cyclopropyl-[2-(4-fluorophenyl)ethyl]carbamoyl}-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK50)**

As for bicyclononene **AK2**, but from bicyclononene **AY3** (590 mg, 0.83 mmol), cyclopropyl-[2-(4-fluorophenyl)ethyl]amine (491 mg, 2.49 mmol), DIPEA (0.568 mL, 3.32 mmol), DMAP (25 mg, 0.21 mmol), HOBt (169 mg, 1.25 mmol) and EDC·HCl (239 mg, 1.25 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (294 mg, 41%). LC-MS: $R_t = 7.93$.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(2-*o*-tolylethyl)carbamoyl]-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK51)**

As for bicyclononene **AK2**, but from bicyclononene **AY3** (590 mg, 0.83 mmol), cyclopropyl-(2-*o*-tolylethyl)amine (491 mg, 2.49 mmol), DIPEA (0.568 mL, 3.32 mmol), DMAP (25 mg, 0.21 mmol), HOBt (169 mg, 1.25 mmol) and EDC·HCl (239 mg, 1.25 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (258 mg, 36%). LC-MS: $R_t = 8.16$.

1:1-Mixture of (*rac.*)-*1R, *5S**)-6-[((*2R**)-2-hydroxy-2-phenylethyl)methylcarbamoyl]-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester and (*rac.*)-(*1R**, *5S**)-6-[((*2S**)-2-hydroxy-2-phenylethyl)methylcarbamoyl]-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK52)**

As for bicyclononene **AK2**, but from bicyclononene **AY3** (590 mg, 0.83 mmol), (*rac.*)-2-methylamino-1-phenylethanol (377 mg, 2.49 mmol), DIPEA (0.568 mL, 3.32 mmol), DMAP (25 mg, 0.21 mmol), HOBt (169 mg, 1.25 mmol) and EDC·HCl (239 mg, 1.25 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compounds (117 mg, 17%). LC-MS: $R_t = 7.50$.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(3,5-dimethoxybenzyl)carbamoyl]-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK53)**

As for bicyclononene **AK2**, but from bicyclononene **AY3** (590 mg, 0.83 mmol), cyclopropyl-(3,5-dimethoxybenzyl)amine (516 mg, 2.49 mmol), DIPEA (0.568 mL, 3.32 mmol), DMAP (25 mg, 0.21 mmol), HOBt (169 mg, 1.25 mmol) and EDC·HCl (239 mg, 1.25 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (258 mg, 35%). LC-MS: $R_t = 7.80$.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(2-*p*-tolylethyl)carbamoyl]-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK54)**

As for bicyclononene **AK2**, but from bicyclononene **AY3** (590 mg, 0.83 mmol), cyclopropyl-(2-*p*-tolylethyl)amine (426 mg, 2.49 mmol), DIPEA (0.568 mL, 3.32 mmol), DMAP (25 mg, 0.21 mmol), HOBt (169 mg, 1.25 mmol) and EDC·HCl (239 mg, 1.25 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (235 mg, 32%). LC-MS: $R_t = 8.16$.

(*rac.*)-(*1R, *5S**)-6-{Cyclopropyl-[2-(2-hydroxyethyl)benzyl]carbamoyl}-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK55)**

As for bicyclononene **AK2**, but from bicyclononene **AY3** (1.18 g, 1.66 mmol), (2-allylbenzyl)cyclopropylamine (932 mg, 4.98 mmol), DIPEA (1.14 mL, 6.64 mmol), DMAP (51 mg, 0.42 mmol), HOBt (338 mg, 2.50 mmol) and EDC·HCl (478 mg, 2.50 mmol) in CH_2Cl_2 (20 mL). Purification by FC yielded the intermediate compound (613 mg, 42%). LC-MS: $R_t = 8.16$.

Then as for compound **AT**, but from the former intermediate compound (613 mg, 0.697 mmol), NMO·H_2O (141 mg, 1.05 mmol), and OsO_4 (2.5% in *tert*-BuOH, 0.175 mL, 0.014 mmol) in THF (8 mL), *tert*-BuOH (4 mL) and water (2 mL). Purification of the residue by FC (EtOAc/heptane 1:1 → EtOAc) yielded the 2nd

intermediate compound (348 mg, 55%). R_f = 0.05 (EtOAc/heptane 1:1). LC-MS: R_t = 7.31.

Then as for compound **AU**, but from the 2nd intermediate compound (348 mg, 0.381 mmol) and $NaIO_4$ (122 mg, 0.571 mmol) in THF (6 mL) and water (2 mL). Drying the residue under high vacuum yielded the 3rd intermediate compound (269 mg, 80%) that was used without further purification. LC-MS: R_t = 7.29.

Finally as for compound **AV**, but from the 3rd intermediate compound (269 mg, 0.305 mmol) and $NaBH_4$ (13 mg, 0.34 mmol) in MeOH (5 mL). Purification of the residue by FC (EtOAc/heptane 1:4 → 2:3 → 3:2 → 4:1) yielded the title compound (210 mg, 78%). LC-MS: R_t = 7.55.

(*rac.*)-(*1R, *5S**)-6-[(2-Chlorobenzyl)cyclopropylcarbamoyl]-7-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK56)**

As for bicyclononene **AK2**, but from bicyclononene **AY4** (596 mg, 0.80 mmol), (2-chlorobenzyl)-cyclopropylamine (290 mg, 1.60 mmol), DIPEA (0.548 mL, 3.2 mmol), DMAP (25 mg, 0.21 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (307 mg, 1.55 mmol) in CH_2Cl_2 (5 mL). Purification by FC yielded the title compound (451 mg, 74%). LC-MS: R_t = 1.30.

(*rac.*)-(*1R, *5S**)-6-[(2-Chlorobenzyl)ethylcarbamoyl]-7-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK57)**

As for bicyclononene **AK2**, but from bicyclononene **AY4** (596 mg, 0.80 mmol), (2-chlorobenzyl)-ethylamine (Ishihara, Y; *et al.*; *Chem. Pharm. Bull.*, **1991**, *39*, 3225; 290 mg, 1.60 mmol), DIPEA (0.548 mL, 3.2 mmol), DMAP (25 mg, 0.21 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (307 mg, 1.55 mmol) in

CH_2Cl_2 (5 mL). Purification by FC yielded the title compound (596 mg, 83%). LC-MS: $R_t = 1.30$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-[cyclopropyl-(2-fluorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK58)**

As for bicyclononene **AK2**, but from bicyclononene **AY4** (596 mg, 0.80 mmol), cyclopropyl-(2-fluorobenzyl)amine (264 mg, 1.60 mmol), DIPEA (0.548 mL, 3.2 mmol), DMAP (25 mg, 0.21 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (307 mg, 1.55 mmol) in CH_2Cl_2 (5 mL). Purification by FC yielded the title compound (519 mg, 73%). LC-MS: $R_t = 1.29$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-[cyclopropyl-(3-trifluoromethylbenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]-non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK59)**

As for bicyclononene **AK2**, but from bicyclononene **AY4** (596 mg, 0.80 mmol), cyclopropyl-(3-trifluoromethylbenzyl)amine (Brabander, H. J.; *et al.*; *J. Org. Chem.*, **1967**, *32*, 4053; 344 mg, 1.60 mmol), DIPEA (0.548 mL, 3.2 mmol), DMAP (25 mg, 0.21 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (307 mg, 1.55 mmol) in CH_2Cl_2 (5 mL). Purification by FC yielded the title compound (584 mg, 78%). LC-MS: $R_t = 1.30$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-[cyclopropyl-(2-methylbenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK60)**

As for bicyclononene **AK2**, but from bicyclononene **AY4** (596 mg, 0.80 mmol), cyclopropyl-(2-methylbenzyl)amine (258 mg, 1.60 mmol), DIPEA (0.548 mL, 3.2 mmol), DMAP (25 mg, 0.21 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (307 mg, 1.55 mmol) in CH_2Cl_2 (5 mL). Purification by FC yielded the title compound (569 mg, 48%). LC-MS: $R_t = 1.30$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(4-methoxyphenoxy)ethyl]carbamoyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK61)**

As for bicyclononene **AK2**, but from bicyclononene **AY4** (596 mg, 0.80 mmol), cyclopropyl-[2-(4-methoxyphenoxy)ethyl]amine (332 mg, 1.60 mmol), DIPEA (0.548 mL, 3.2 mmol), DMAP (25 mg, 0.21 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (307 mg, 1.55 mmol) in CH_2Cl_2 (5 mL). Purification by FC yielded the title compound (591 mg, 79%). LC-MS: $R_t = 1.28$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(3-methoxyphenoxy)ethyl]carbamoyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK62)**

As for bicyclononene **AK2**, but from bicyclononene **AY4** (596 mg, 0.80 mmol), cyclopropyl-[2-(3-methoxyphenoxy)ethyl]amine (332 mg, 1.60 mmol), DIPEA (0.548 mL, 3.2 mmol), DMAP (25 mg, 0.21 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (307 mg, 1.55 mmol) in CH_2Cl_2 (5 mL). Purification by FC yielded the title compound (584 mg, 77%). LC-MS: $R_t = 1.28$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-[cyclopropyl-(2-*m*-tolyloxyethyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK63)**

As for bicyclononene **AK2**, but from bicyclononene **AY4** (596 mg, 0.80 mmol), cyclopropyl-(2-*p*-tolyloxyethyl)amine (306 mg, 1.60 mmol), DIPEA (0.548 mL, 3.2 mmol), DMAP (25 mg, 0.21 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (307 mg, 1.55 mmol) in CH_2Cl_2 (5 mL). Purification by FC yielded the title compound (525 mg, 71%). LC-MS: R_t = 1.30.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-(cyclopropylphenethylcarbamoyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK64)**

As for bicyclononene **AK2**, but from bicyclononene **AY4** (596 mg, 0.80 mmol), cyclopropyl-phenethylamine (Smith, P. W.; *et al.*; *J. Med. Chem.*, **1998**, *41*, 787; 258 mg, 1.60 mmol), DIPEA (0.548 mL, 3.2 mmol), DMAP (25 mg, 0.21 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (307 mg, 1.55 mmol) in CH_2Cl_2 (5 mL). Purification by FC yielded the title compound (360 mg, 50%). LC-MS: R_t = 1.30.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-{[2-(2-chlorophenyl)ethyl]cyclopropylcarbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (AK65)**

As for bicyclononene **AK2**, but from bicyclononene **AY4** (596 mg, 0.80 mmol), [2-(2-chloro-phenyl)ethyl]cyclopropylamine (313 mg, 1.60 mmol), DIPEA (0.548 mL, 3.2 mmol), DMAP (25 mg, 0.21 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (307 mg, 1.55 mmol) in CH_2Cl_2 (5 mL). Purification by FC yielded the title compound (572 mg, 76%). LC-MS: R_t = 1.30.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(2,3-difluorophenyl)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]-

non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK66)

As for bicyclononene **AK2**, but from bicyclononene **AY4** (596 mg, 0.80 mmol), cyclopropyl-[2-(2,3-difluorophenyl)ethyl]amine (316 mg, 1.60 mmol), DIPEA (0.548 mL, 3.2 mmol), DMAP (25 mg, 0.21 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (307 mg, 1.55 mmol) in CH_2Cl_2 (5 mL). Purification by FC yielded the title compound (584 mg, 79%). LC-MS: $R_t = 1.29$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(4-fluorophenyl)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (AK67)**

As for bicyclononene **AK2**, but from bicyclononene **AY4** (596 mg, 0.80 mmol), cyclopropyl-[2-(4-fluorophenyl)ethyl]amine (287 mg, 1.60 mmol), DIPEA (0.548 mL, 3.2 mmol), DMAP (25 mg, 0.21 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (307 mg, 1.55 mmol) in CH_2Cl_2 (5 mL). Purification by FC yielded the title compound (616 mg, 84%). LC-MS: $R_t = 1.28$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-[cyclopropyl-(2-*o*-tolylethyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK68)**

As for bicyclononene **AK2**, but from bicyclononene **AY4** (596 mg, 0.80 mmol), cyclopropyl-(2-*o*-tolylethyl)amine (280 mg, 1.60 mmol), DIPEA (0.548 mL, 3.2 mmol), DMAP (25 mg, 0.21 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (307 mg, 1.55 mmol) in CH_2Cl_2 (5 mL). Purification by FC yielded the title compound (556 mg, 76%). LC-MS: $R_t = 1.28$.

1:1-Mixture of (*rac.*)-(*1R, *5S**)-7-{4-[2-(2-chloro-4,5-dimethylphenoxy)-ethoxy]phenyl}-6-[((*2R**)-2-hydroxy-2-phenylethyl)methylcarbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester and (*rac.*)-(*1R**, *5S**)-7-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-[((*2S**)-2-hydroxy-2-phenylethyl)methyl-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK69)**

As for bicyclononene **AK2**, but from bicyclononene **AY4** (596 mg, 0.80 mmol), (*rac.*)-2-methylamino-1-phenylethanol (242 mg, 1.60 mmol), DIPEA (0.548 mL, 3.2 mmol), DMAP (25 mg, 0.21 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (307 mg, 1.55 mmol) in CH_2Cl_2 (5 mL). Purification by FC yielded the title compounds (380 mg, 54%). LC-MS: R_t = 1.23.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-[cyclopropyl-(3,5-dimethoxybenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (AK70)**

As for bicyclononene **AK2**, but from bicyclononene **AY4** (596 mg, 0.80 mmol), cyclopropyl-(3,5-dimethoxybenzyl)amine (332 mg, 1.60 mmol), DIPEA (0.548 mL, 3.2 mmol), DMAP (25 mg, 0.21 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (307 mg, 1.55 mmol) in CH_2Cl_2 (5 mL). Purification by FC yielded the title compound (619 mg, 83%). LC-MS: R_t = 1.28.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-[cyclopropyl-(2-*p*-tolylethyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK71)**

As for bicyclononene **AK2**, but from bicyclononene **AY4** (596 mg, 0.80 mmol), cyclopropyl-(2-*p*-tolylethyl)amine (280 mg, 1.60 mmol), DIPEA (0.548 mL, 3.2

mmol), DMAP (25 mg, 0.21 mmol), HOBt (135 mg, 1.00 mmol) and EDC·HCl (307 mg, 1.55 mmol) in CH_2Cl_2 (5 mL). Purification by FC yielded the title compound (619 mg, 83%). LC-MS: $R_t = 1.28$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(2-hydroxyethyl)benzyl]carbamoyl}-3,9-diazabicyclo[3.3.1]-non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (AK72)**

As for bicyclononene **AK2**, but from bicyclononene **AY3** (1.00 g, 1.34 mmol), (2-allylbenzyl)cyclopropylamine (752 mg, 4.02 mmol), DIPEA (0.918 mL, 5.26 mmol), DMAP (41 mg, 0.34 mmol), HOBt (199 mg, 1.47 mmol) and EDC·HCl (385 mg, 2.01 mmol) in CH_2Cl_2 (15 mL). Purification by FC yielded the intermediate compound (845 mg, 69%). $R_f = 0.45$ (EtOAc/heptane 1:1). LC-MS: $R_t = 7.85$.

Then as for compound **AT**, but from the former intermediate compound (845 mg, 0.926 mmol), NMO·H_2O (150 mg, 1.11 mmol), and OsO_4 (2.5% in *tert*-BuOH, 0.173 mL, 0.014 mmol) in THF (8 mL), *tert*-BuOH (4 mL) and water (2 mL). Purification of the residue by FC (EtOAc/heptane 1:1 → EtOAc → MeOH/EtOAc 1:9) yielded the 2nd intermediate compound (616 mg, 70%). $R_f = 0.05$ (EtOAc/heptane 1:1). LC-MS: $R_t = 7.04$.

Then as for compound **AU**, but from the 2nd intermediate compound (616 mg, 0.649 mmol) and $NaIO_4$ (208 mg, 0.973 mmol) in THF (6 mL) and water (2 mL). Drying the residue under high vacuum yielded the 3rd intermediate compound (477 mg, 80%) that was used without further purification. LC-MS: $R_t = 7.43$.

Finally as for compound **AV**, but from the 3rd intermediate compound (477 mg, 0.520 mmol) and $NaBH_4$ (22 mg, 0.57 mmol) in MeOH (5 mL). Purification of the residue by FC (EtOAc/heptane 1:4 → 2:3 → 3:2 → 4:1) yielded the title compound (210 mg, 78%). $R_f = 0.10$ (EtOAc/heptane 1:1). LC-MS: $R_t = 7.26$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-[(2-chlorobenzyl)cyclopropylcarbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK73)**

As for bicyclononene **AK2**, but from bicyclononene **AY5** (534 mg, 0.7 mmol), (2-chlorobenzyl)-cyclopropylamine (200 mg, 1.10 mmol), DIPEA (0.479 mL, 2.8 mmol), DMAP (21 mg, 0.18 mmol), HOBt (113 mg, 0.84 mmol) and EDC·HCl (211 mg, 1.1 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (263 mg, 39%). LC-MS: $R_t = 1.28$.

(*rac.*)-(*1R, *5S**)-6-(Benzylcyclopropylcarbamoyl)-7-{4-[2-(4-bromophenoxy)-ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK74)**

As for bicyclononene **AK2**, but from bicyclononene **AY5** (534 mg, 0.7 mmol), benzylcyclopropyl-amine (Loeppky, R. N.; *et al.*, *J. Org. Chem.*, **2000**, *65*, 96; 162 mg, 1.10 mmol), DIPEA (0.479 mL, 2.8 mmol), DMAP (21 mg, 0.18 mmol), HOBt (113 mg, 0.84 mmol) and EDC·HCl (211 mg, 1.1 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (263 mg, 39%). LC-MS: $R_t = 1.26$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-[(2-chlorobenzyl)ethylcarbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK75)**

As for bicyclononene **AK2**, but from bicyclononene **AY5** (534 mg, 0.7 mmol), (2-chlorobenzyl)-ethylamine (Ishihara, Y; *et al.*; *Chem. Pharm. Bull.*, **1991**, *39*, 3225; 187 mg, 1.10 mmol), DIPEA (0.479 mL, 2.8 mmol), DMAP (21 mg, 0.18 mmol), HOBt (113 mg, 0.84 mmol) and EDC·HCl (211 mg, 1.1 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (204 mg, 32%). LC-MS: $R_t = 1.28$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-[cyclopropyl-(2-fluorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK76)**

As for bicyclononene **AK2**, but from bicyclononene **AY5** (534 mg, 0.7 mmol), cyclopropyl-(2-fluorobenzyl)amine (182 mg, 1.10 mmol), DIPEA (0.479 mL, 2.8 mmol), DMAP (21 mg, 0.18 mmol), HOBt (113 mg, 0.84 mmol) and EDC·HCl (211 mg, 1.1 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (233 mg, 37%). LC-MS: $R_t = 1.27$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-[cyclopropyl-(3-trifluoromethylbenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK77)**

As for bicyclononene **AK2**, but from bicyclononene **AY5** (534 mg, 0.7 mmol), cyclopropyl-(3-trifluoromethylbenzyl)amine (Brabander, H. J.; *et al.*; *J. Org. Chem.*, **1967**, *32*, 4053; 237 mg, 1.10 mmol), DIPEA (0.479 mL, 2.8 mmol), DMAP (21 mg, 0.18 mmol), HOBt (113 mg, 0.84 mmol) and EDC·HCl (211 mg, 1.1 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (276 mg, 41%). LC-MS: $R_t = 1.27$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-[cyclopropyl-(2-methylbenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK78)**

As for bicyclononene **AK2**, but from bicyclononene **AY5** (534 mg, 0.7 mmol), cyclopropyl-(2-methylbenzyl)amine (178 mg, 1.10 mmol), DIPEA (0.479 mL, 2.8 mmol), DMAP (21 mg, 0.18 mmol), HOBt (113 mg, 0.84 mmol) and EDC·HCl (211 mg, 1.1 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (171 mg, 27%). LC-MS: $R_t = 1.26$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(4-methoxyphenoxy)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK79)**

As for bicyclononene **AK2**, but from bicyclononene **AY5** (534 mg, 0.7 mmol), cyclopropyl-[2-(4-methoxyphenoxy)ethyl]amine (228 mg, 1.10 mmol), DIPEA (0.479 mL, 2.8 mmol), DMAP (21 mg, 0.18 mmol), HOBt (113 mg, 0.84 mmol) and EDC·HCl (211 mg, 1.1 mmol) in CH_2Cl_2 (7 mL). Purification by FC yielded the title compound (190 mg, 29%). LC-MS: R_t = 1.26.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(3,4-dimethylphenoxy)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK80)**

As for bicyclononene **AK2**, but from bicyclononene **AY5** (700 mg, 0.918 mmol), cyclopropyl-[2-(3,4-dimethylphenoxy)ethyl]amine (565 mg, 2.75 mmol), DIPEA (0.628 mL, 3.67 mmol), DMAP (28 mg, 0.23 mmol), HOBt (136 mg, 1.01 mmol) and EDC·HCl (264 mg, 1.38 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (199 mg, 23%). LC-MS: R_t = 7.76.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-{[2-(2-chloro-phenyl)ethyl]cyclopropylcarbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK81)**

As for bicyclononene **AK2**, but from bicyclononene **AY5** (700 mg, 0.918 mmol), [2-(2-chloro-phenyl)ethyl]cyclopropylamine (538 mg, 2.75 mmol), DIPEA (0.628 mL, 3.67 mmol), DMAP (28 mg, 0.23 mmol), HOBt (136 mg, 1.01 mmol) and EDC·HCl (264 mg, 1.38 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (256 mg, 30%). LC-MS: R_t = 7.70.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(2,3-difluorophenyl)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK82)**

As for bicyclononene **AK2**, but from bicyclononene **AY5** (700 mg, 0.918 mmol), cyclopropyl-[2-(2,3-difluorophenyl)ethyl]amine (542 mg, 2.75 mmol), DIPEA (0.628 mL, 3.67 mmol), DMAP (28 mg, 0.23 mmol), HOBt (136 mg, 1.01 mmol) and EDC·HCl (264 mg, 1.38 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (245 mg, 28%). LC-MS: $R_t = 7.55$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(4-fluorophenyl)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK83)**

As for bicyclononene **AK2**, but from bicyclononene **AY5** (700 mg, 0.918 mmol), cyclopropyl-[2-(4-fluorophenyl)ethyl]amine (493 mg, 2.75 mmol), DIPEA (0.628 mL, 3.67 mmol), DMAP (28 mg, 0.23 mmol), HOBt (136 mg, 1.01 mmol) and EDC·HCl (264 mg, 1.38 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (220 mg, 26%). LC-MS: $R_t = 7.51$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-[cyclopropyl-(2-*o*-tolylethyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK84)**

As for bicyclononene **AK2**, but from bicyclononene **AY5** (700 mg, 0.918 mmol), cyclopropyl-(2-*o*-tolylethyl)amine (482 mg, 2.75 mmol), DIPEA (0.628 mL, 3.67 mmol), DMAP (28 mg, 0.23 mmol), HOBt (136 mg, 1.01 mmol) and EDC·HCl (264 mg, 1.38 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (252 mg, 30%). LC-MS: $R_t = 7.66$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-[cyclopropyl-(3,5-dimethoxybenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxy-lic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK85)**

As for bicyclononene **AK2**, but from bicyclononene **AY5** (700 mg, 0.918 mmol), Cyclopropyl-(3,5-dimethoxy-benzyl)-amine (570 mg, 2.75 mmol), DIPEA (0.628 mL, 3.67 mmol), DMAP (28 mg, 0.23 mmol), HOBt (136 mg, 1.01 mmol) and EDC·HCl (264 mg, 1.38 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (242 mg, 28%). LC-MS: $R_t = 7.42$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-[cyclopropyl-(2-*p*-tolylethyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK86)**

As for bicyclononene **AK2**, but from bicyclononene **AY5** (700 mg, 0.918 mmol), cyclopropyl-(2-*p*-tolylethyl)amine (482 mg, 2.75 mmol), DIPEA (0.628 mL, 3.67 mmol), DMAP (28 mg, 0.23 mmol), HOBt (136 mg, 1.01 mmol) and EDC·HCl (264 mg, 1.38 mmol) in CH_2Cl_2 (10 mL). Purification by FC yielded the title compound (246 mg, 29%). LC-MS: $R_t = 7.66$.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(2-hydroxyethyl)benzyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AK87)**

As for bicyclononene **AK2**, but from bicyclononene **AY5** (1.00 g, 1.31 mmol), (2-allylbenzyl)cyclopropylamine (752 mg, 4.02 mmol), DIPEA (0.918 mL, 5.26 mmol), DMAP (41 mg, 0.34 mmol), HOBt (199 mg, 1.47 mmol) and EDC·HCl (385 mg, 2.01 mmol) in CH_2Cl_2 (15 mL). Purification by FC yielded the

intermediate compound (875 mg, 72%). R_f = 0.45 (EtOAc/heptane 1:1). LC-MS: R_t = 7.69.

Then as for compound **AT**, but from the former intermediate compound (875 mg, 0.939 mmol), NMO·H_2O (152 mg, 1.13 mmol), and OsO_4 (2.5% in *tert*-BuOH, 0.236 mL, 0.019 mmol) in THF (8 mL), *tert*-BuOH (4 mL) and water (2 mL). Purification of the residue by FC (EtOAc/heptane 1:1 → EtOAc → MeOH/EtOAc 1:9) yielded the 2nd intermediate compound (310 mg, 34%). R_f = 0.05 (EtOAc/heptane 1:1). LC-MS: R_t = 6.86.

Then as for compound **AU**, but from the 2nd intermediate compound (310 mg, 0.321 mmol) and $NaIO_4$ (139 mg, 0.481 mmol) in THF (6 mL) and water (2 mL). Drying the residue under high vacuum yielded the 3rd intermediate compound (239 mg, 80%) that was used without further purification. LC-MS: R_t = 7.29.

Finally as for compound **AV**, but from the 3rd intermediate compound (239 mg, 0.256 mmol) and $NaBH_4$ (11 mg, 0.28 mmol) in MeOH (5 mL). Purification of the residue by FC (EtOAc/heptane 1:4 → 2:3 → 3:2 → 4:1) yielded the title compound (170 mg, 71%). R_f = 0.10 (EtOAc/heptane 1:1). LC-MS: R_t = 7.13.

Compounds of type AL

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Bromo-5-fluorophenoxy)ethyl]phenyl}-6-(methyl-phenethylcarbamoyl)-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL1)**

A sol. bicyclononene **AK1** (540 mg, 0.61 mmol)I in CH_2Cl_2 (10 mL) was cooled to 0°C. HCl/dioxane (4M, 10 mL) was added and the ice bath was removed. After 4 h stirring at rt the solvents were removed under reduced pressure and the residue dried under high vacuum. The crude was used without further purification.

(*rac.*)-(*1R, *5S**)-6-[(2-Chlorobenzyl)cyclopropylcarbamoyl]-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethyl-ethyl ester hydrochloride salt (AL2)**

As for compound **AL1** but from bicyclononene **AK2** (407 mg, 0.47 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.06; ES+: 796.34.

(*rac.*)-(*1R, *5S**)-6-(Benzylcyclopropylcarbamoyl)-7-{4-[3-(2,3,6-trifluoro-phenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethyl-ethyl ester hydrochloride salt (AL3)**

As for compound **AL1** but from bicyclononene **AK3** (570 mg, 0.65 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.04; ES+: 766.34.

(*rac.*)-(*1R, *5S**)-6-[(2-Chlorobenzyl)ethylcarbamoyl]-7-{4-[3-(2,3,6-trifluoro-phenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL4)**

As for compound **AL1** but from bicyclononene **AK4** (about 0.55 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.19; ES+: 786.25.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(2-fluorobenzyl)carbamoyl]-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL5)**

As for compound **AL1** but from bicyclononene **AK5** (about 0.55 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.18; ES+: 782.28.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(3-trifluoromethylbenzyl)carbamoyl]-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL6)**

As for compound **AL1** but from bicyclononene **AK6** (about 0.55 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.20.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(2-methylbenzyl)carbamoyl]-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL7)**

As for compound **AL1** but from bicyclononene **AK7** (about 0.55 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.21; ES+: 778.30.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(4-methoxyphenoxymethyl)carbamoyl]-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL8)**

As for compound **AL1** but from bicyclononene **AK8** (about 0.55 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.21.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(3-methoxyphenoxymethyl)carbamoyl]-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL9)**

As for compound **AL1** but from bicyclononene **AK9** (about 0.55 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.18.

(*rac.*)-(*1R, *5S**)-6-(Cyclopropyl-*m*-tolyloxymethylcarbamoyl)-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL10)**

As for compound **AL1** but from bicyclononene **AK10** (about 0.55 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.24.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(3,4-dimethylphenoxymethyl)carbamoyl]-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL11)**

As for compound **AL1** but from bicyclononene **AK11** (about 0.55 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.28.

(*rac.*)-(*1R, *5S**)-6-(Cyclopropylphenethylcarbamoyl)-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL12)**

As for compound **AL1** but from bicyclononene **AK12** (about 0.55 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.18; ES+: 778.30.

(*rac.*)-(*1R, *5S**)-6-{[2-(2-Chlorophenyl)ethyl]cyclopropylcarbamoyl}-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL13)**

As for compound **AL1** but from bicyclononene **AK13** (about 0.55 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.21.

(*rac.*)-(*1R, *5S**)-6-{Cyclopropyl-[2-(2,3-difluorophenyl)ethyl]carbamoyl}-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (AL14)**

As for compound **AL1** but from bicyclononene **AK14** (about 0.55 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.21.

(*rac.*)-(*1R, *5S**)-6-{Cyclopropyl-[2-(4-fluorophenyl)ethyl]carbamoyl}-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL15)**

As for compound **AL1** but from bicyclononene **AK15** (about 0.55 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.18; ES+: 796.28.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(2-*o*-tolylethyl)carbamoyl]-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL16)**

As for compound **AL1** but from bicyclononene **AK16** (about 0.55 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.21; ES+: 794.30.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(3,5-dimethoxybenzyl)carbamoyl]-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL17)**

As for compound **AL1** but from bicyclononene **AK17** (about 0.55 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.16.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(2-*p*-tolylethyl)carbamoyl]-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL18)**

As for compound **AL1** but from bicyclononene **AK18** (about 0.55 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.22; ES+: 792.30.

(*rac.*)-(*1R, *5S**)-6-{Cyclopropyl-[2-(2-hydroxyethyl)benzyl]carbamoyl}-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-**

9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL19)

As for compound **AL1** but from bicyclononene **AK19** (about 0.55 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.01.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-[(2-chlorobenzyl)cyclopropylcarbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL20)**

As for compound **AL1** but from bicyclononene **AK20** (about 0.55 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 5.26; ES+: 806.26.

(*rac.*)-(*1R, *5S**)-6-(Benzylcyclopropylcarbamoyl)-7-{4-[3-(2-bromo-5-fluoro-phenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL21)**

As for compound **AL1** but from bicyclononene **AK21** (519 mg, 0.54 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.06.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-[(2-chlorobenzyl)ethylcarbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL22)**

As for compound **AL1** but from bicyclononene **AK22** (about 0.8 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 5.30; ES+: 828.33.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-[cyclopropyl-(2-fluorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL23)**

As for compound **AL1** but from bicyclononene **AK23** (about 0.8 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL).

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-[cyclopropyl-(3-trifluoromethylbenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL24)**

As for compound **AL1** but from bicyclononene **AK24** (about 0.8 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 5.33; ES+: 820.40.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-[cyclopropyl-(2-methylbenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL25)**

As for compound **AL1** but from bicyclononene **AK25** (about 0.8 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.06.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-{cyclopropyl-[2-(4-methoxyphenoxy)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL26)**

As for compound **AL1** but from bicyclononene **AK26** (about 0.8 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 5.08; ES+: 866.40.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-[cyclopropyl-(2-*m*-tolyloxyethyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL27)**

As for compound **AL1** but from bicyclononene **AK27** (about 0.8 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.07.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-{cyclopropyl-[2-(3,4-dimethylphenoxy)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]-non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL28)**

As for compound **AL1** but from bicyclononene **AK28** (about 0.8 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.08.

-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-(cyclopropylphenethylcarbamoyl)-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL29)**

As for compound **AL1** but from bicyclononene **AK29** (about 0.8 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 5.25; ES+: 820.38.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-{[2-(2-chlorophenyl)ethyl]cyclopropylcarbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL30)**

As for compound **AL1** but from bicyclononene **AK30** (about 0.8 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 5.35; ES+: 854.30.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-{cyclopropyl-[2-(2,3-difluorophenyl)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL31)**

As for compound **AL1** but from bicyclononene **AK31** (about 0.8 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 5.40; ES+: 856.38.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-{cyclopropyl-[2-(4-fluorophenyl)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL32)**

As for compound **AL1** but from bicyclononene **AK32** (about 0.8 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 5.28; ES+: 838.40.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-[cyclopropyl-(2-*o*-tolylethyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL33)**

As for compound **AL1** but from bicyclononene **AK33** (about 0.8 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 5.36; ES+: 834.42.

1:1-Mixture of (*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]-phenyl}-6-[((*2R**)-2-hydroxy-2-phenylethyl)methylcarbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt and (*rac.*)-(*1R**, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-[((*2S**)-2-hydroxy-2-phenylethyl)methylcarbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL34)**

As for compound **AL1** but from bicyclononenes **AK34** (about 0.3 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 0.99.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-[cyclopropyl-(3,5-dimethoxybenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-**

carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL35)

As for compound **AL1** but from bicyclononene **AK35** (about 0.8 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 5.23; ES+: 866.40.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-[cyclopropyl-(2-*p*-tolylethyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL36)**

As for compound **AL1** but from bicyclononene **AK36** (about 0.8 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 5.59; ES+: 834.42.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-{cyclopropyl-[2-(2-hydroxyethyl)benzyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL37)**

As for compound **AL1** but from bicyclononene **AK37** (about 0.8 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.01.

(*rac.*)-(*1R, *5S**)-6-[(2-Chlorobenzyl)cyclopropylcarbamoyl]-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL38)**

As for compound **AL1** but from bicyclononene **AK38** (312 mg, 0.35 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.08; ES+: 774.33.

(*rac.*)-(*1R, *5S**)-6-(Benzylcyclopropylcarbamoyl)-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL39)**

As for compound **AL1** but from bicyclononene **AK39** (340 mg, 0.40 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.05; ES+: 740.42.

(*rac.*)-(*1R, *5S**)-6-[(2-Chlorobenzyl)ethylcarbamoyl]-7-{4-[2-(2,3,6-trimethyl-phenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL40)**

As for compound **AL1** but from bicyclononene **AK40** (374 mg, 0.43 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.07; ES+: 762.34.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(2-fluorobenzyl)carbamoyl]-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL41)**

As for compound **AL1** but from bicyclononene **AK41** (350 mg, 0.41 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.06; ES+: 758.38.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(3-trifluoromethylbenzyl)carbamoyl]-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL42)**

As for compound **AL1** but from bicyclononene **AK42** (294 mg, 0.32 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.08.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(2-methylbenzyl)carbamoyl]-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL43)**

As for compound **AL1** but from bicyclononene **AK43** (322 mg, 0.38 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.08; ES+: 752.39.

(*rac.*)-(*1R, *5S**)-6-{Cyclopropyl-[2-(4-methoxyphenoxy)ethyl]carbamoyl}-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL44)**

As for compound **AL1** but from bicyclononene **AK44** (159 mg, 0.18 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.07.

(*rac.*)-(*1R, *5S**)-6-{Cyclopropyl-[2-(3-methoxyphenoxy)ethyl]carbamoyl}-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (AL45)**

As for compound **AL1** but from bicyclononene **AK45** (237 mg, 0.26 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.00.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(2-*m*-tolyloxyethyl)carbamoyl]-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxy-lic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL46)**

As for compound **AL1** but from bicyclononene **AK46** (185 mg, 0.21 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.09; ES+: 784.40.

(*rac.*)-(*1R, *5S**)-6-(Cyclopropylphenethylcarbamoyl)-7-{4-[2-(2,3,6-trimethyl-phenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL47)**

As for compound **AL1** but from bicyclononene **AK47** (about 0.3 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.09; ES+: 754.44.

(*rac.*)-(*1R, *5S**)-6-{[2-(2-Chlorophenyl)ethyl]cyclopropylcarbamoyl}-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL48)**

As for compound **AL1** but from bicyclononene **AK48** (about 0.3 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.10; ES+: 788.41.

(*rac.*)-(*1R, *5S**)-6-{Cyclopropyl-[2-(2,3-difluorophenyl)ethyl]carbamoyl}-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL49)**

As for compound **AL1** but from bicyclononene **AK49** (about 0.3 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.09; ES+: 788.41.

(*rac.*)-(*1R, *5S**)-6-{Cyclopropyl-[2-(4-fluorophenyl)ethyl]carbamoyl}-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL50)**

As for compound **AL1** but from bicyclononene **AK50** (about 0.3 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.09; ES+: 772.41.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(2-*o*-tolylethyl)carbamoyl]-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL51)**

As for compound **AL1** but from bicyclononene **AK51** (about 0.3 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.10; ES+: 768.44.

1:1-Mixture of (*rac.*).-(*1R, *5S**)-6-[((*2S**)-2-hydroxy-2-phenylethyl)methylcarbamoyl]-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt and (*rac.*)-(*1R**, *5S**)-6-[((*2S**)-2-hydroxy-2-phenylethyl)-methylcarbamoyl]-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL52)**

As for compound **AL1** but from bicyclononene **AK52** (about 0.3 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.02; ES+: 744.44.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(3,5-dimethoxybenzyl)carbamoyl]-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL53)**

As for compound **AL1** but from bicyclononene **AK53** (about 0.3 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.07.

(*rac.*)-(*1R, *5S**)-6-[Cyclopropyl-(2-*p*-tolylethyl)carbamoyl]-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL54)**

As for compound **AL1** but from bicyclononene **AK54** (about 0.3 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.10; ES+: 768.44.

(*rac.*)-(*1R, *5S**)-6-{Cyclopropyl-[2-(2-hydroxyethyl)benzyl]carbamoyl}-7-{4-[2-(2,3,6-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL55)**

As for compound **AL1** but from bicyclononene **AK55** (about 0.3 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.03; ES+: 784.44.

(*rac.*)-(*1R, *5S**)-6-[(2-Chlorobenzyl)cyclopropylcarbamoyl]-7-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL56)**

As for compound **AL1** but from bicyclononene **AK56** (about 0.5 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.08; ES+: 785.26.

(*rac.*)-(*1R, *5S**)-6-[(2-Chlorobenzyl)ethylcarbamoyl]-7-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL57)**

As for compound **AL1** but from bicyclononene **AK57** (about 0.5 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.06.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-[cyclopropyl-(2-fluorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL58)**

As for compound **AL1** but from bicyclononene **AK58** (about 0.5 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.06.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-[cyclopropyl-(3-trifluoromethylbenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]-non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL59)**

As for compound **AL1** but from bicyclononene **AK59** (about 0.5 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.08.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-[cyclopropyl-(2-methylbenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL60)**

As for compound **AL1** but from bicyclononene **AK60** (about 0.5 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.07; ES+: 788.40.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(4-methoxyphenoxy)ethyl]carbamoyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL61)**

As for compound **AL1** but from bicyclononene **AK61** (about 0.5 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.06.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(3-methoxyphenoxy)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL62)**

As for compound **AL1** but from bicyclononene **AK62** (about 0.5 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.07.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-[cyclopropyl-(2-*m*-tolyloxyethyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL63)**

As for compound **AL1** but from bicyclononene **AK63** (about 0.5 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.08.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-(cyclopropylphenethylcarbamoyl)-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL64)**

As for compound **AL1** but from bicyclononene **AK64** (about 0.5 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.07; ES+: 788.39.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-{[2-(2-chlorophenyl)ethyl]cyclopropylcarbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL65)**

As for compound **AL1** but from bicyclononene **AK65** (about 0.5 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.08.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(2,3-difluorophenyl)ethyl]carbamoyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL66)**

As for compound **AL1** but from bicyclononene **AK66** (about 0.5 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.06.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(4-fluorophenyl)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL67)**

As for compound **AL1** but from bicyclononene **AK67** (about 0.5 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.06.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-[cyclopropyl-(2-*o*-tolylethyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (AL68)**

As for compound **AL1** but from bicyclononene **AK68** (about 0.5 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.08.

1:1-Mixture of (*rac.*)-(*1R, *5S**)-7-{4-[2-(2-chloro-4,5-dimethylphenoxy)-ethoxy]phenyl}-6-[((*2R**)2-hydroxy-2-phenylethyl)methylcarbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt and (*rac.*)-(*1R**, *5S**)-7-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-[((*2S**)2-hydroxy-2-phenylethyl)methylcarbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL69)**

As for compound **AL1** but from bicyclononene **AK69** (about 0.5 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 0.99; ES+: 780.37.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-[cyclopropyl-(3,5-dimethoxybenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL70)**

As for compound **AL1** but from bicyclononene **AK70** (about 0.5 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.06.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-[cyclopropyl-(2-*p*-tolylethyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-**

carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL71)

As for compound **AL1** but from bicyclononene **AK71** (about 0.5 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.08.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(2-hydroxyethyl)benzyl]carbamoyl}-3,9-diazabicyclo[3.3.1]-non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt**

As for compound **AL1** but from bicyclononene **AK72** (about 0.5 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.01.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-[(2-chloro-benzyl)cyclopropylcarbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethyl-ethyl ester hydrochloride salt (AL73)**

As for compound **AL1** but from bicyclononene **AK73** (0.28 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 4.98; ES+: 824.32.

(*rac.*)-(*1R, *5S**)-6-(Benzylcyclopropylcarbamoyl)-7-{4-[2-(4-bromophenoxy)-ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL74)**

As for compound **AL1** but from bicyclononene **AK74** (0.27 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 1.03; ES+: 792.36.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-[(2-chloro-benzyl)ethylcarbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL75)**

As for compound **AL1** but from bicyclononene **AK75** (0.22 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 4.92; ES+: 812.35.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-[cyclopropyl-(2-fluorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL76)**

As for compound **AL1** but from bicyclononene **AK76** (0.26 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 4.78; ES+: 808.40.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-[cyclopropyl-(3-trifluoromethylbenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL77)**

As for compound **AL1** but from bicyclononene **AK77** (0.29 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 4.97; ES+: 858.42.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-[cyclopropyl-(2-methylbenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL78)**

As for compound **AL1** but from bicyclononene **AK78** (0.28 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 5.01; ES+: 804.42.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(4-methoxyphenoxy)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL79)**

As for compound **AL1** but from bicyclononene **AK79** (0.2 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 5.03; ES+: 850.44.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(3,4-dimethylphenoxy)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL80)**

As for compound **AL1** but from bicyclononene **AK80** (0.21 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 5.11; ES+: 848.43.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-{[2-(2-chlorophenyl)ethyl]cyclopropylcarbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL81)**

As for compound **AL1** but from bicyclononene **AK81** (0.27 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 5.09; ES+: 838.36.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(2,3-difluorophenyl)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL82)**

As for compound **AL1** but from bicyclononene **AK82** (0.26 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 4.44; ES+: 840.42.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(4-fluorophenyl)ethyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL83)**

As for compound **AL1** but from bicyclononene **AK83** (0.24 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 4.89; ES+: 822.39.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-[cyclopropyl-(2-*o*-tolylethyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL84)**

As for compound **AL1** but from bicyclononene **AK84** (0.27 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL).

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-[cyclopropyl-(3,5-dimethoxybenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL85)**

As for compound **AL1** but from bicyclononene **AK85** (0.25 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 4.76; ES+: 850.40.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-[cyclopropyl-(2-*p*-tolylethyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL86)**

As for compound **AL1** but from bicyclononene **AK86** (0.27 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 4.99; ES+: 820.78.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-6-{cyclopropyl-[2-(2-hydroxyethyl)benzyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester hydrochloride salt (AL87)**

As for compound **AL1** but from bicyclononene **AK87** (0.18 mmol) in CH_2Cl_2 (5 mL) and HCl/dioxane (4M, 5 mL). LC-MS: R_t = 4.58; ES+: 834.43.

(*rac.*)-(*1R, *5S**)-7-Hydroxy-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 6-benzyl ester 3-*tert*-butyl ester (AM)**

$Ti(OEt)_4$ (2.92 mL, 13.9 mmol) was added to a sol. of bicyclononane A (13.0 g, 39.8 mmol) in benzyl alcohol (90 mL). The mixture was heated to 125 °C and stirred at this temperature for 28 h. The mixture was allowed to cool to rt and aq. 10% HCl (180 mL) was added. The mixture was extracted with Et_2O (3x). The combined org. extracts were washed with aq. $NaHCO_3$ (2x), with brine (1x). The org. extracts were then dried over $MgSO_4$, filtered, and the solvents were removed first under reduced pressure, then under high vacuum. Purification of the residue by FC (EtOAc/heptane 1:1 → 3:1 → EtOAc) yielded the title compound (9.90 g, 64%). LC-MS: R_t = 1.39; ES+: 389.25.

(*rac.*)-(*1R, *5S**)-9-Methyl-7-trifluoromethanesulfonyloxy-3,9-diazabicyclo-[3.3.1]non-6-ene-3,6-dicarboxylic acid 6-benzyl ester 3-*tert*-butyl ester (AN)**

NaH (55% in oil, 2.20 g, 50.5 mmol) was added to a sol. of bicyclononane **AM** (15.69 g, 40.4 mmol) in THF (290 mL) at 0°C. After 15 min. Tf_2NPh (19.2 g, 53.7 mmol) was added and the mixture was stirred overnight while warming up to rt. Ice was added and the mixture was diluted with EtOAc, and washed with aq. 10% Na_2CO_3. The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:1 → 3:1) yielded the title compound (17.1 g, 81%). R_f = 0.15 (EtOAc/heptane 1:1). LC-MS: R_t = 5.62; ES+: 521.37.

Compounds of type AO

(*rac.*)-(*1R, *5S**)-7-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 6-benzyl ester 3-*tert*-butyl ester (AO1)**

BuLi (1.5M in hexane, 3.81 mL, 5.71 mmol) was added to a sol. of [3-(4-bromophenyl)propoxy]-*tert*-butyldimethylsilane (Kiesewetter D. O., *Tetrahedron Asymmetry*, **1993**, *4*, 2183, 1.88 g, 5.71 mmol) in THF (33 mL) at –78 °C. After

30 min $ZnCl_2$ (1M in THF, 6.97 mL, 6.97 mmol, prepared as described for compound **G1**) was added and the mixture was allowed to warm up to rt. Bicyclononene **AN** (1.65 g, 3.17 mmol) and $Pd(PPh_3)_4$ (92 mg, 0.080 mmol) were added. The mixture was heated to 40 °C and stirred at this temperature for 30 min. The mixture was allowed to cool to rt and aq. 1M HCl (1 mL) was added. The mixture was diluted with EtOAc and washed with aq. 1M NaOH (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC ($MeOH/CH_2Cl_2$ 1:49 → 3:97 → 2:48 → 5:95) yielded the title compound (1.78 g, 90%). LC-MS: R_t = 5.55; ES+: 681.30.

(*rac.*)-(*1R, *5S**)-9-Methyl-7-{4-[2-(2,3,5-trimethylphenoxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 6-benzyl ester 3-*tert*-butyl ester (AO2)**

BuLi (1.6M in hexane, 19.40 mL, 31.0 mmol) was added to a sol. of compound **C2** (9.90 g, 31.0 mmol) in THF (100 mL) at –78 °C. After 30 min $ZnCl_2$ (0.83M in THF, 43.8 mL, 37.2 mmol, prepared as described for compound **G1**) was added and the mixture was allowed to warm up to rt. Bicyclononene **AN** (9.90 g, 19.0 mmol) and $Pd(PPh_3)_4$ (550 mg, 0.475 mmol) were added. The mixture was heated to reflux for 1 h. The mixture was allowed to cool to rt and aq. 1M HCl (1 mL) was added. The mixture was diluted with EtOAc and washed with aq. 1M NaOH (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC ($MeOH/CH_2Cl_2$ 1:49 → 3:97 → 2:48 → 5:95) yielded the title compound (6.20 g, 54%). LC-MS: R_t = 5.10; ES+: 611.59.

Compounds of type AP

(*rac.*)-(*1R, *5S**)-7-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 6-benzyl ester 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AP1)**

A sol. of bicyclononene **AO1** (1.78 g, 2.87 mmol) and 2,2,2-trichloro-*tert*-butyl chloroformate (3.44 g, 14.4 mmol) in CH_2ClCH_2Cl (35 mL) was heated to reflux for 2 h. The mixture was allowed to cool to rt and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:8 → 1:1) yielded the title compound (1.88 g, 81%). LC-MS: R_t = 8.34.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2,3,5-Trimethylphenoxy)ethyl]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 6-benzyl ester 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AP2)**

As for compound **AP1** but from bicyclononene **AO2** (22.4 g, 36.7 mmol) and 2,2,2-trichloro-*tert*-butyl chloroformate (44 g, 184 mmol) in CH_2ClCH_2Cl (400 mL). Purification of the residue by FC (EtOAc/heptane 1:8 → 1:1) yielded the title compound (19.2 g, 65%). LC-MS: R_t = 7.95.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-[4-(3-hydroxypropyl)phenyl]-3,9-diazabicyclo-[3.3.1]non-6-ene-6,9-dicarboxylic acid 6-benzyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AQ)**

HCl/dioxane (4M, 20 mL) was added to a sol. of bicyclononene **AP1** (1.88 g, 2.32 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C. The ice bath was removed and the mixture was stirred for 3 h at rt. The solvents were removed under reduced pressure and the residue was dried under high vacuum. This residue was then dissolved in THF (30 mL) and the sol. was cooled to –78 °C. DMAP (cat. amount), DIPEA (1.60 mL, 9.28 mmol) and AcCl (0.165 mL, 2.32 mmol) were added. The mixture was stirred for 15 min at –78 °C and MeOH(10 mL) was added. The mixture was allowed to warm up to rt, was dissolved in EtOAc and washed with aq. 1M HCl (1x) and aq. sat. $NaHCO_3$ (1x). The org. Extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1...4 → 1:1 →

EtOAc → MeOH/EtOAc 1:9) yielded the title compound (936 mg, 63%). LC-MS: R_t = 5.47; ES+: 637.06.

Compounds of type AR

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 6-benzyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AR1)**

A mixture of bicyclononene **AQ** (468 mg, 0.73 mmol), 2,3,6-trifluorophenol (216 mg, 1.46 mmol), azodicarboxylic dipiperidide (277 mg, 1.10 mmol) and tributyl phosphine (0.541 mL, 2.19 mmol) in toluene (15 mL) was heated to reflux for 20 h. The mixture was allowed to cool to rt and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:49 → 1:19 → 1:9) yielded the title compound (297 mg, 53%). LC-MS: R_t = 6.87; ES+: 767.04.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 6-benzyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AR2)**

As for the bicyclononene **AR1**, but from bicyclononene **AQ1** (468 mg, 0.73 mmol), 2-bromo-5-fluorophenol (0.163 mL, 1.46 mmol), azodicarboxylic dipiperidide (277 mg, 1.10 mmol) and tributyl phosphine (0.541 mL, 2.19 mmol) in toluene (15 mL). Purification of the residue by FC (EtOAc/heptane 1:49 → 1:19 → 1:9) yielded the title compound (205 mg, 35%). LC-MS: R_t = 7.06.

(*rac.*)-(*1R, *5S**)-3-Acetyl-6-[(2-allylbenzyl)cyclopropylcarbamoyl]-7-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (AS)**

A mixture of bicyclononene **AJ4** (225 mg, 0.300 mmol), (2-allylbenzyl)-cyclopropylamine (168 mg, 0.900 mmol), DIPEA (0.300 mL, 1.80 mmol), DMAP (10 mg, 0.082 mmol), HOBt (41 mg, 0.300 mmol) and EDC.HCl (86 mg, 0.450 mmol) in CH_2Cl_2 (3 mL) was stirred for 2 days. EDC.HCl (29 mg, 0.150 mmol) was added again after 24 h and 30 h. The mixture was diluted with CH_2Cl_2 and washed with aq. 1M HCl (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 3:7 → 2:3 → 1:1 → 3:2 → 7:3 → 4:1) yielded the title compound (185 mg, 67%). R_f = 0.63 (EtOAc). LC-MS: R_t = 7.40.

1:1-Mixture of (*rac.*)-(*1R, *5S**)-3-acetyl-7-{4-[3-(2-bromo-5-fluorophenoxy)-propyl]phenyl}-6-{cyclopropyl-[2-((*2R**)-2,3-dihydroxypropyl)benzyl]-carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester and (*rac.*)-(*1R**, *5S**)-3-acetyl-7-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-6-{cyclopropyl-[2-((*2S**)-2,3-dihydroxypropyl)benzyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (AT)**

A mixture of bicyclononene **AS** (281 mg, 0.316 mmol), $NMO{\cdot}H_2O$ (44.8 mg, 0.332 mmol), and OsO_4 (2.5% in *tert*-BuOH, 0.0396 mL, 0.00316 mmol) in THF (4 mL), *tert*-BuOH (2 mL) and water (1 mL) was stirred overnight. $NMO{\cdot}H_2O$ (10 mg, 0.074 mmol) and OsO_4 (0.010 mL, 0.008 mmol) were added again and the mixture was stirred again for 3 h. The solvents were removed under reduced pressure, and the residue was diluted with EtOAc, washed with aq. 1M HCl (1x), and with aq. sat. NaHCO3 (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 2:3 → 3:2 → 4:1 → EtOAc → MeOH/EtOAc 1:9) yielded the title compounds (207 mg, 71%). R_f = 0.20 (EtOAc). LC-MS: R_t = 6.23; ES+: 922.59.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-6-{cyclopropyl-[2-(2-oxoethyl)benzyl]carbamoyl}-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (AU)**

A mixture of bicyclononenes **AT** (167 mg, 0.181 mmol) and $NaIO_4$ (40 mg, 0.187 mmol) in THF (3 mL) and water (1 mL) was stirred at rt for 1 h. NaIO4 (20 mg, 0.01 mmol) was added again and the mixture was stirred for 3 h. The mixture was diluted with EtOAc and washed with aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was dried under high vacuum and the title compound (156 mg, 97%) was used without further purification. LC-MS: R_t = 6.87; ES+: 891.78.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-{4-[3-(2-bromo-5-fluorophenoxy)propyl]phenyl}-6-{cyclopropyl-[2-(2-hydroxyethyl)benzyl]carbamoyl}-3,9-diazabicyclo[3.3.1]-non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (AV)**

A mixture of bicyclononene **AU** (44.6 mg, 0.05 mmol) and $NaBH_4$ (about 2 mg, about 0.05 mmol) in MeOH (1 mL) was stirred at rt for 90 min. The mixture was diluted with EtOAc and washed with aq. 1M HCl (1x). The org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The residue was used without further purification.

Compounds of type AW

(*rac.*)-(*1R, *5S**)-7-[4-(3-Hydroxypropyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AW1)**

TBAF (28.8 g, 91.4 mmol) was added to a sol. of bicyclononene **H3** (45.6 g, 60.9 mmol) in THF (900 mL) at 0 °C. After 20 min, the ice bath was removed. After stirring the mixture at rt for 5 h, it was diluted with EtOAc and washed with water

(2x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 1:1) yielded the title compound (27.6 g, 72%). R_f = 0.22 (EtOAc/heptane 1:1). LC-MS: R_t = 6.11; ES+: 655.23.

(*rac.*)-(*1R, *5S**)-7-[4-(2-Hydroxyethoxy)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AW2)**

As for compound **AW1** but from bicyclononene **H7** (44.4 g, 59.2 mmol) TBAF (28.0 g, 88.9 mmol) and THF (600 mL). Purification by FC (EtOAc/heptane 1:3 → 1:1 → EtOAc) yielded the title compound (23.67 g, 63%). R_f = 0.20 (EtOAc/heptane 1:1). LC-MS: R_t = 6.02; ES+: 635.36.

Compounds of type AX

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AX1)**

A mixture of bicyclononene **AW1** (20.22 g, 32.0 mmol), 2,3,6-trifluorophenol (9.50 g, 64.0 mmol), azodicarboxylic dipiperidide (16.15 g, 64.0 mmol) and tributyl phosphine (85%, 27.9 mL, 96.0 mmol) in toluene (800 ml) was heated to reflux for 2 h. The mixture was allowed to cool to rt and the solvent removed under reduced pressure. Purification of the residue was purified by FC (EtOAc/heptane 1:19 → 1:9 → 1:4) yielded the title compound (21.7 g, 89%). R_f = 0.60 (EtOAc/heptane 1:1). LC-MS: R_t = 1.25; ES+: 765.22.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AX2)**

As for **AX1**, but from bicyclononene **AW1** (27.63 g, 43.6 mmol), 2-bromo-5-fluorophenol (9.70 mL, 87.2 mmol), azodicarboxylic dipiperidide (22.0 g, 87.2 mmol), tributyl phosphine (32.2 mL, 131 mmol), and toluene (550 ml). Purification of the residue by FC (EtOAc/heptane 1:19 → 1:9 → 1:4) yielded the title compound (31.67 g, 90%). R_f = 0.60 (EtOAc/heptane 1:1). LC-MS: R_t = 7.63.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AX3)**

As for **AX1**, but from bicyclononene **AW2** (11.83 g, 18.6 mmol), 2-chloro-4,5-dimethylphenol (5.83 mL, 37.2 mmol), azodicarboxylic dipiperidide (9.39 g, 37.2 mmol), tributyl phosphine (85%, 16.2 mL, 55.8 mmol), and toluene (300 ml). Purification of the residue by FC (EtOAc/heptane 1:19 → 1:9 → 1:3 → 1:1) yielded the title compound (13.35 g, 93%). R_f = 0.50 (EtOAc/heptane 1:1). LC-MS: R_t = 7.60.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-6,9-dicarboxylic acid 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AX4)**

As for **AX1**, but from bicyclononene **AW2** (11.83 g, 18.6 mmol), 4-bromophenol (6.43 mL, 37.2 mmol), azodicarboxylic dipiperidide (9.39 g, 37.2 mmol), tributyl phosphine (85%, 16.2 mL, 55.8 mmol), and toluene (300 ml). Purification of the residue by FC (EtOAc/heptane 1:19 → 1:9 → 1:3 → 1:1) yielded the title compound (13.6 g, 92%). R_f = 0.50 (EtOAc/heptane 1:1). LC-MS: R_t = 7.49.

Compounds of type AY

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AY1)**

A mixture of bicyclononene **AX1** (15.76 g, 20.7 mmol) in EtOH (600 mL) and aq. 1M NaOH (600 mL) was stirred for 7 h at 80 °C. The mixture was allowed to cool to rt and the solvents were partially removed under reduced pressure. The residue was diluted with EtOAc and aq. 1M HCl was added to pH 1 - 2. The phases were shaken, separated and the aq. phase was extracted with EtOAc (2x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 1:2 → 1:1) yielded the title compound (12.15 g, 80%). LC-MS: R_t = 1.16; ES+: 737.21.

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AY2)**

As for compound **AY1**, but from bicyclononene **AX2** (29.67 g, 36.8 mmol), EtOH (700 mL) and aq. 1M NaOH (700 mL). Purification by FC (EtOAc/heptane 1:1 → EtOAc → MeOH/EtOAc 1:9) yielded the title compound 26.67 g (94%). LC-MS: R_t = 6.89; ES+: 749.92.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2,3,5-Trimethylphenoxy)ethyl]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AY3)**

Under N_2 Pd/C (10%, 1.92 g) was added to a sol. of bicyclononene **AP2** (19.2 g, 24.0 mmol) in MeOH (390 mL) cooled to 0 °C. The mixture was purged with H_2 (4x) and stirred at 0 °C under H_2 for 7 h. The mixture was filtered through *Celite*, diluted with EtOAc and washed with aq. 1M HCl (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced

pressure. Purification by FC (EtOAc/heptane 1:3 → 1:1 → EtOAc → MeOH/EtOAc 1:9) yielded the title compound (4.26 g, 25%). LC-MS: R_t = 7.10.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AY4)**

As for compound **AY1**, but from bicyclononene **AX3** (13.35 g, 17.2 mmol), EtOH (670 mL) and aq. 1M NaOH (670 mL). Purification by FC (EtOAc/heptane 1:1 → EtOAc → MeOH/EtOAc 1:9) yielded the title compound 12.3 g (96%). R_f = 0.75 (EtOAc). LC-MS: R_t = 6.94.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(4-Bromophenoxy)ethoxy]phenyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AY5)**

As for compound **AY1**, but from bicyclononene **AX4** (13.6 g, 17.2 mmol), EtOH (680 mL) and aq. 1M NaOH (680 mL). Purification by FC (EtOAc/heptane 1:1 → EtOAc → MeOH/EtOAc 1:9) yielded the title compound 12.2 g (93%). R_f = 0.75 (EtOAc). LC-MS: R_t = 6.75.

Compounds of type AZ

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-[4-(3-hydroxypropyl)phenyl]-3,9-diazabicyclo-[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AZ1)**

A mixture of bicyclononene **S5** (3.23 g, 5.60 mmol) in EtOH (50 mL) and aq. 1M NaOH (50 mL) was stirred at 80 °C for 5 h. The mixture was allowed to cool to rt and diluted with EtOAc. The mixture was brought to pH 2 with aq. 1M HCl and extracted with EtOAc (3x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by

FC ($MeOH/CH_2Cl_2$ 1:19 → 1:9 → 1:4) yielded the title compound (1.40 g, 46%). LC-MS: R_t = 0.89; ES+: 547.28.

(*rac.*)-(*1R, *5S**)-7-[4-(2-Hydroxyethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (AZ2)**

As for compound **AZ1** but from bicyclononene **H8** (4.96 g), EtOH (150 mL) and aq. 1M NaOH (150 mL). The crude material was used further without purification.

Compounds of type BA

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-{4-[3-(*tert*-butyldimethylsilanyloxy)propyl]-phenyl}-6-[(2-chlorobenzyl)cyclopropylcarbamoyl]-3,9-diazabicyclo[3.3.1]-non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (BA1)**

A mixture of bicyclononene **T4** (1.85 g, 2.79 mmol), (2-chlorobenzyl)-cyclopropylamine (1.52 g, 8.37 mmol), DMAP (85 mg, 0.70 mmol), DIPEA (1.91 mL, 11.2 mmol), HOBt (377 mg, 2.79 mmol) and EDC·HCl (803 mg, 4.19 mmol) in CH_2Cl_2 (50 mL) was stirred at rt for 18 h. The mixture was diluted with more CH_2Cl_2 and washed with aq. 1M HCl (1x) and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 1:3 → 1:2 → 1:1) yielded the title compound (1.16 g, 50%). LC-MS: R_t = 1.37.

(*rac.*)-(*1R, *5S**)-7-{4-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]phenyl}-6-[(2-chlorobenzyl)cyclopropylcarbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (BA2)**

As for compound **BA1**, bur from bicyclononene **T5** (crude, about 5.79 mmol), (2-chlrobenzyl)cyclopropylamine (3.10 g, 17.1 mmol), DIPEA (3.9 mL, 22.8 mmol), DMAP (140 mg, 1.14 mmol), HOBt (770 mg, 5.70 mmol), and EDC·HCl (1.64 g, 8.55 mmol), in CH_2Cl_2 (50 mL). Purification of the residue by FC (EtOAc/heptane 1:8 → 1:4) yielded the title compound 3.35 g (58%). $R_f = 0.55$ (EtOAc/heptane 2:3). LC-MS: $R_t = 1.40$.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-{4-[2-(*tert*-butyldiphenylsilanyloxy)ethyl]phenyl}-6-[(2-chlorobenzyl)cyclopropylcarbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (BA3)**

As for compound **S1**, from **BA2** (1.45 g, 1.45 mmol), CH_2Cl_2 (10 mL), 4M HCl/dioxane (10 mL), THF (20 mL), without DMAP, DIPEA (4.62 mL, 27.0 mmol), acetyl chloride (0.903 mL,9.55 mmol), and MeOH (5 mL). Purification of the residue by FC (ErOAc/heptane 1:1 → EtOAc → MeOH/EtOAc 1:9) led to the title compound (1.34 g, 75%). Rf = 0.30 (EtOAc/heptane 1:1). LC-MS: R_t = 1.39.

Compounds of type BB

(*rac.*)-(*1R, *5S**)-3-Acetyl-6-[(2-chlorobenzyl)cyclopropylcarbamoyl]-7-[4-(3-hydroxypropyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (BB1)**

A mixture of bicyclononene **BA1** (1.16 g, 1.40 mmol) and TBAF (884 mg, 2.80 mmol) in THF (10 mL) was stirred at rt for 90 min. The mixture was diluted with EtOAc and washed with water (2x) and brine (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by FC (MeOH/CH_2Cl_2 1:49 → 1:9) yielded the title compound (990 mg, 98%). $R_f = 0.47$ (MeOH/CH_2Cl_2 1:9). LC-MS: $R_t = 1.11$.

(*rac.*)-(*1R, *5S**)-3-Acetyl-6-[(2-chlorobenzyl)cyclopropylcarbamoyl]-7-[4-(2-hydroxyethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-9-carboxylic acid 2,2,2-trichloro-1,1-dimethylethyl ester (BB2)**

As for compound **BB1**, but from **BA3** (1.99 g, 2.21 mmol), TBAF (1M in THF, 4.5 mL, 4.5 mmol) in THF (15 mL). Purification by FC (EtOAc/heptane 1:5 → 1:1 → EtOAc) yielded the title compound (1.00 g, 68%). R_f = 0.38 (EtOAc/heptane 1:1). LC-MS: R_t = 1.09; ES+: 698.02.

(*rac.*)-(*1R, *5S**)-6-[(2-Chlorobenzyl)cyclopropylcarbamoyl]-7-{4-[3-(2,3,6-trifluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3-carboxylic acid *tert*-butyl ester (BC)**

Zn (1.63 g, 24.9 mmol) was added to a sol. of bicyclononene **AK2** (2.25 g, 2.50 mmol) in THF (30 mL) and AcOH (10 mL) under efficient stirring. The mixture was stirred efficiently for 2.5 h, then filtered and washedwith THF. The filtrate was diluted with EtOAc and washed with aq. 1M NaHO (2x). The org. extracts were dried over $MgSO_4$, and filtered. Evaporating the solvents under reduced pressure yielded the title compound that was used without further purification.

(*1R*, *5S*)-9-Methyl-7-trifluoromethanesulfonyloxy-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 6-benzyl ester 3-*tert*-butyl ester (BD)

A sol. of bicyclononene **AG** (1.13 g; 2.91 mmol) in THF (8 ml) was added to a suspension of NaH (ca 60%, 175 mg; 4.36 mmol) in THF (2 ml) at 0°C. After 30 min Tf_2NPh (1.56 g; 4.36 mmol) was added and the mixture was stirred at rt for 12 h. Ice (5 g) was added and THF was evaporated. The aq. residue was extracted with EtOAc (3x). The combine org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Puriciation of the residue by FC (EtOAc/cyclohexane 1:1 → EtOAc) yielded the title compound (1.28 g, 84%). R_f = 0.53 (EtOAc).

(*1R*, *5S*)-7-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 6-benzyl ester 3-*tert*-butyl ester (BE)

BuLi (1.6 M in hexane, 3.82 mL, 5.98 mmol) was added to a sol. of [3-(4-bromophenyl)propoxy]-*tert*-butyldimethylsilane (Kiesewetter D. O., *Tetrahedron Asymmetry*, **1993**, *4*, 2183; 1.97 g; 5.98 mmol) in THF (4ml) at -78°C. After 30 min, $ZnCl_2$ (1M in THF, 7.2 ml; 7.2 mmol) was added and the mixture was alloed to warm up to rt. A sol. of bicyclononene **BD** (1.24 g: 2.39 mmol) in THF (7 ml) and $Pd(PPh_3)_4$ (69 mg; 0.060 mmol) were added after each other and the mixture was heated to 40°C for 35 min. The reaction mixture was allowed to cool to rt, sat. solution of NH_4Cl was added, and the mixture was extracted with EtOAc (3x). The combined org. extracts were dried over $MgSO_4$,filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/cyclohexane 1:1 → EtOAc) yielded the title compound (1.22 g, 82%). R_f = 0.27 (EtOAc). LC-MS: R_t = 5.68; ES+ = 621.30.

(*1R*, *5S*)-7-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 6-benzyl ester 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (BF)

A mixture of bicyclononene **BE** (1.66 g, 2.67 mmol) and β,β,β-trichloro-*tert*-butyl chloroformate (13.4 g, 240 mmol) in 1,2-dichloroethane (10 ml) was heated to reflux for 4 h. The mixture was allowed to cool to rt and the solvents were removed under reduced pressure. Purification of the residue by FC EtOAc/cyclohexane 1:4) yielded the title compound (1.75 g, 83%). R_f = 0.43 (EtOAc/cyclohexane 1:4). LC-MS: R_t = 8.30.

(*1R*, *5S*)-7-[4-(3-Hydroxypropyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 6-benzyl ester 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (BH)

A sol. of bicyclononene **BF** (1.59 g, 1.96 mmol) in CH_2Cl_2 (3 ml) was cooled to 0°C and HCl/dioxane (4M, 10 ml) was added. The mixture was stirred for 2 h at 0°C and subsequently for 3 h at rt. After the solvents were removed under reduced pressure the crude was dried under high vacuum. The cresidue was dissolved in THF (5 ml). DMAP (12 mg, 0.098 mmol) and DIPEA (1.34 ml; 7.849 mmol) were added and the mixture was cooled to –78 °C. AcCl (0.153 ml; 2.16 mmol) was added and reaction mixture was stirred at –78 °C for 30 min. After addition of MeOH (1 ml) and warming-up to rt, aq. HCl (1M, 10 ml) was added and reaction mixture was extracted with EtOAc (3x). The combined org. extracts were washed with aq. sat. $NaHCO_3$ (1x), and the org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC EtOAc/cyclohexane 1:3 → 1:1) yielded the title compound (280 mg, 22%). R_f = 0.38 (EtOAc). LC-MS: R_t = 5.43; ES+ = 637.17.

(*1R*, *5S*)-7-[4-(3-Hydroxypropyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (BI)

A mixture of bicyclononene **BH** (140 mg; 0.219 mmol) and Pd/C (10%, 25 mg) in MeOH (4 ml) was stitted at rt under H_2 for 2 h. The mixture was filtered through *Celite*, washed with MeOH, and the solvents were evaporated under reduced pressure. The crude product (110 mg) was directly used in the next reaction without purification. R_f = 0.15 (EtOAc). LC-MS: R_t = 4.41; ES- : 545.02.

(*1R*, *5S*)-7-[4-(3-Hydroxypropyl)phenyl]-6-(methylphenethylcarbamoyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (BJ)

A mixture of bicyclononene **BI** (95 mg; 0.17 mmol), phenethylmethylamine (0.48 ml; 0.34 mmol); HOBt (6.0 mg, 0.042 mmol), EDC·HCl (49 mg; 0.255 mmol) and DMAP (5.0 mg; 0.042 mmol) in $CHCl_3$ (6 ml) was stirred at rt for 14 h. Aq HCl (1M) was added and the mixture was extracted with CH_2Cl_2 (3x). The org. phase

was washed with aq. sat. $NaHCO_3$ (1x), the combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/cyclohexane 1:1 → EtOAc) yielded the title compound (64 mg, 44%). R_f = 0.25 (EtOAc). LC-MS: R_t = 5.37; ES+: 664.29.

(*1R*, *5S*)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-(methyl-phenethylcarbamoyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid 3-*tert*-butyl ester 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (BK)

A mixture of bicyclononene **BJ** (60 mg; 0.090 mmol), 2-bromo-5-fluorophenol (34 mg, 0.18 mmol), azodicarboxylic dipiperidide (34 mg; 0.135 mmol) and tributylphosphine (67 mg; 0.270 mmol) in toluene (2 ml) was heated to reflux for 20 h. The solvent was removed under reduced pressure. Purification of the residue was by FC EtOAc/cyclohexane 2:1 → 4:1) yielded the title compound (58 mg, 76%). R_f = 0.60 (EtOAc). LC-MS: R_t = 7.01; ES+ = 836.07.

(*rac.*)-(*1R, *5S**)-3-Acetyl-7-{4-[3-(2-bromo-5-fluorophenoxy)-propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (BL)**

HCl/dioxane (4M, 20 mL) was added to a sol. of bicyclononene **AX2** (2.00 g, 2.47 mmol) in CH_2Cl_2 (20 mL) cooled to 0 °C. The ice bath removed and the mixture was stirred at rt for 2 h. The solvents were removed under reduced pressure and the foamy residue dried under high vacuum. A mixture of this residue, DMAP (15 mg, 0.123 mmol) and DIPEA (1.69 mL, 9.88 mmol) in THF (40 mL) was cooled to -78 °C, and AcCl (0.186 mL, 2.47 mmol) was added. The mixture was stirred for 20 min at -78 °C and MeOH (5 mL) was added. The mixture was allowed to warm up to rt, was diluted with EtOAc and washed with aq. 1M HCl (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC

(EtOAc/heptane 1:4 → 1:1 → EtOAc) yielded the title compound (1.55 g, 83%). R_f = 0.50 (EtOAc).

Compounds of type BM

3-Acetyl-7-{4-[2-(2-bromo-5-fluorophenoxy)ethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (BM2)

Tributylphosphine (3.84 mL, 15.6 mmol) was added to a sol. of bicyclononene **S4** (3.00 g, 5.19 mmol), 2-bromo-5-fluorophenol (1.15 mL, 10.4 mmol) and azodicarboxylic dipiperidide (1.97 g, 7.79 mmol) in toluene (30 mL). The mixture was heated to reflux for 2 h and allowed to cool to rt. The solvents were removed under reduced pressure. Purification by FC (EtOAc/heptane 1:1 → 2:1 → 3:1) yielded the title compound (2.70 g, 69%).

3-Acetyl-7-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (BM3)

As described for compound **BM2**, but from bicyclononene **S4** (3.00 g, 5.19 mmol), 2-chloro-4,5-dimethylphenol (1.64 g, 10.5 mmol), azodicarboxylic dipiperidide (1.98 g, 7.86 mmol) , tributylphosphine (3.90 mL, 15.7 mmol) and toluene (50 mL). Purification by FC yielded the title compound (2.82 g, 75%).

3-Acetyl-7-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (BM4)

As described for compound **BM2**, but from bicyclononene **S4** (3.00 g, 5.19 mmol), 2,6-dichloro-4-methylphenol (1.84 g, 10.38 mmol), azodicarboxylic

dipiperidide (1.97 g, 7.79 mmol) , tributylphosphine (3.84 mL, 15.6 mmol) and toluene (50 mL). Purification by FC yielded the title compound (2.76 g, 72%).

3-Acetyl-7-{4-[2-(2,3-dichlorophenoxy)ethoxy]phenyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-6,9-dicarboxylic acid 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (BM5)

As described for compound **BM2**, but from bicyclononene **S4** (3.20 g, 5.54 mmol), 2,3-dichlorophenol (1.80 g, 11.1 mmol), azodicarboxylic dipiperidide (2.10 g, 8.31 mmol) , tributylphosphine (4.11 mL, 16.6 mmol) and toluene (50 mL). Purification by FC yielded the title compound (2.22 g, 55%).

3-Acetyl-7-{4-[2-(4-chloro-2-methylphenoxy)ethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (BM7)

As described for compound **BM2**, but from bicyclononene **S4** (3.00g, 5.19 mmol), 4-chloro-2-methylphenol (1.48 g, 10.4 mmol), azodicarboxylic dipiperidide (1.97 g, 7.79 mmol) , tributylphosphine (3.84 mL, 15.6 mmol) and toluene (50 mL). Purification by FC yielded the title compound (1.36 g, 37%).

3-Acetyl-7-{4-[2-(2,4,5-trichlorophenoxy)ethoxy]phenyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-6,9-dicarboxylic acid 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (BM9)

As described for compound **BM2**, but from bicyclononene **S4** (3.00 g, 5.19 mmol) 2,4,5-trichlorophenol (2.05 g, 10.4 mmol), azodicarboxylic dipiperidide (1.97 g, 7.79 mmol) , tributylphosphine (3.84 mL, 15.6 mmol) and toluene (50 mL). Purification by FC yielded the title compound (2.76 g, 72%).

3-Acetyl-7-{4-[2-(2-chloro-5-fluorophenoxy)ethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 6-ethyl ester 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (BM10)

As described for compound **BM2**, but from bicyclononene **S4** (3.18 g, 5.50 mmol) 2-chloro-5-fluorophenol (1.61 g, 11.0 mmol), azodicarboxylic dipiperidide (2.08 g, 8.25 mmol) , tributylphosphine (4.10 mL, 16.6 mmol) and toluene (50 mL). Purification by FC yielded the title compound (2.67 g, 69%).

Compounds of type BN

3-Acetyl-7-{4-[2-(2-bromo-5-fluorophenoxy)ethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (BN2)

A mixture of bicyclononene **BM2** (2.69, 3.58 mmol) in aq. 1M NaOH (30 mL) and EtOH (70 mL) was stirred for 1 h at 85 °C. The mixture was allowed to cool to rt and the solvents were partially removed under reduced pressure. The residue was acidified to pH 2 with aq. 1M HCl and this mixture was extracted with EtOAc (3x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The crude title compound (2.96 g, quantitative yield) was used further without purification.

3-Acetyl-7-{4-[2-(2-chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (BN3)

As described for compound **BN2**, but from bicyclononene **BM3** (2.82 g, 3.94 mmol), aq. 1M NaOH (30 mL) and EtOH (70 mL). The crude title compound (2.59 g, 96%) was used further without purification.

3-Acetyl-7-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (BN4)

As described for compound **BN2**, but from bicyclononene **BM4** (2.75 g, 3.73 mmol), aq. 1M NaOH (30 mL) and EtOH (70 mL). The crude title compound (2.63 g, quantitative yield) was used further without purification.

3-Acetyl-7-{4-[2-(2,3-dichlorophenoxy)ethoxy]phenyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (BN5)

As described for compound **BN2**, but from bicyclononene **BM5** (2.22 g, 3.07 mmol), aq. 1M NaOH (30 mL) and EtOH (70 mL). The crude title compound (1.59 g, 75%) was used further without purification.

3-Acetyl-7-{4-[2-(4-chloro-2-methylphenoxy)ethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-(2,2,2-trichloro-1,1-dimethyl-ethyl) ester (BN7)

As described for compound **BN2**, but from bicyclononene **BM7** (1.35 g, 1.92 mmol), aq. 1M NaOH (30 mL) and EtOH (70 mL). The crude title compound (1.25 g, 97%) was used further without purification.

3-Acetyl-7-{4-[2-(2,4,5-trichlorophenoxy)ethoxy]phenyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (BN9)

As described for compound **BN2**, but from bicyclononene **BM9** (2.31 g, 3.05 mmol), aq. 1M NaOH (30 mL) and EtOH (70 mL). The crude title compound (2.19 g, 99%) was used further without purification.

3-Acetyl-7-{4-[2-(2-chloro-5-fluorophenoxy)ethoxy]phenyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-(2,2,2-trichloro-1,1-dimethylethyl) ester (BN10)

As described for compound **BN2**, but from bicyclononene **BM10** (2.82 g, 3.94 mmol), aq. 1M NaOH (30 mL) and EtOH (70 mL). The crude title compound (1.90 g, 74%) was used further without purification.

Preparation of the final compounds

Typical procedure (A) for the acylation:

To a solution of bicyclononene in anhydrous EtOAc was added vacuum dried-Amberlyst 21 (1.5 g/mmole of bicyclononene) or another suitable scavenger, followed by the addition of the desired acid chloride (1.5 eq.). After shaking the suspension for 3 h, an aliquot water was added and shaking was continued for 1 h. The resin was then removed by filtration, washed with EtOAc and the filtrate was evaporated to yield the intermediate amide.

The synthesis of the sulfonamide, carbamate or urea derivatives was performed in analogy to the above-described procedure, by using the corresponding sulfonyl chloride, chloroformate or carbamoyl chloride respectively.

Typical procedure (B) for amide formation from acid chlorides:

To a sol. of the acid chloride (1 eq.) in CH_2Cl_2 (2.5 mL/mmol) at 0 °C. the amine (3 eq.) was added. The mixture was stirred for 3 h while warming up slowly to rt. If necessary, more CH_2Cl_2 was added, then the reaction mixture was washed with aq. sat. $NaHCO_3$ (1x) and aq. 1M HCl (1x). The extracts were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The obtained product was used without further purification.

Typical procedure (C) for an amide coupling with CDI

To a sol. of the carboxylic acid (1 eq.) in CH_2Cl_2 (4 mL/mmol) CDI (1 eq.) was added. The sol. or suspension was stirred for 2 h at rt, then cooled to 0 °C. The amine (6 eq.) was added and the sol. or suspension was stirred for 2 h while warming up slowly to rt. The sol. or suspension was washed with water (1x). The org. extracts were evaporated under reduced pressure and the obtained residue was used further without purification.

Typical procedure (D) for the reduction of an amide to an amine with LAH

To a sol. of the amide (1 eq.) was dissolved in THF (3 mL/mmol) LAH (1M in THF, 3 eq.) was added carefully. The mixture was stirred at rt for 30 min, then heated to 60 °C for 3 h before it was allowed to cool down to rt, then to 0 °C. For x g of $LiAlH_4$ initially added, was added x g of water, then x g of aq. 15% NaOH, and finally 3x g of water again. The resulting mixture was stirred overnight, filtered, and the precipitate washed with EtOAc. The filtrate was evaporated under reduced pressure and the residue diluted in a small amount of MeOH. The sol. was passed through a pad of SCX silica gel (sulfonic acid). Elution started with MeOH, followed by NH_3/MeOH. The amines eluted with the second second eluent. The solvents were removed under reduced pressure. The isolated amines were either used without further purification or purified by HPLC, depending on the purity.

Typical procedure (E) for the cleavage of the 2,2,2-trichloro-1,1-dimethylethylcarbamate protecting group:

The crude product from another typical procedure was dissolved in THF/AcOH (1:0.1) and treated with zinc (20 eq.). The suspension was stirred for 5 h and filtered through celite, which was washed with EtOAc. The filtrate was evaporated under reduced pressure and the residue was purified by HPLC.

Typical procedure (F) for the formation of aryl ether (Mitsunobu reaction)

The bicyclononene (0.05 mmol) was dissolved or suspended in toluene (1.00 mL). The phenol derivative (0.075 mmol) in toluene (0.50 mL) was added. TMAD (0.075 mmol) in toluene (0.50 mL) was added, followed by tributylphosphine (0.15 mmol). The reaction mixture was stirred for 2 h at rt and then 2 h at 60 °C. Sometimes, it was necessary to add a second portion of tributylphosphine and to stir overnight. Sometimes, THF was necessary as cosolvent to dissolve the reactants. The reaction mixture was allowed to cool to rt, then water was added. The mixture was extracted with EtOAc, and the org. extracts were evaporated under reduced pressure.

Typical procedure (G) for an amide coupling

To a sol. of bicyclononene (0.05 mmol) in $CHCl_3$ (2 mL) the desired carboxylic acid (0.10 mmol) was added. DIPEA (0.10 mmol), DMAP (0.01 mmol), HOBt (0.01 mmol), and EDC·HCl (0.05 mmol) were added and the reaction mixture was stirred overnight. Sometimes, it was necessary to add another portion of acid, DMAP, HOBt and EDC·HCl and to continue stirring for 24 h. CH_2Cl_2 was added and the mixture was washed with water. The org. extracts were separated, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure.

Typical procedure (H) for an amide coupling

To a sol. of the bicyclononene (0.05 mmol) $CHCl_3$ or CH_2Cl_2 (2 mL) the desired amine (commercially available or prepared following known, standard procedures) (0.10 mmol) was added. DIPEA (0.10 mmol), DMAP (0.01 mmol), HOBt (0.01 mmol) and EDC·HCl (0.05 mmol) were added. The reaction mixture was stirred overnight. Sometimes, it was necessary to add another portion of amine, DMAP, HOBt and EDC·HCl and to continue stirring the sol. for 24 h. CH_2Cl_2 was added and the mixture was washed with water. The org. extracts

were separated, dried over Na_2SO_4 and filtered. The solvents were removed under reduced pressure.

Typical procedure (J) for reductive amination

To a solution of aldehyde (1eq.) in MeOH (0.5 mL/mmol) was added an amine (1.2 eq.). The solution was stirred for 2h. Sodium borohydride (1.2 eq.) was added portionwise at 0°C and then stirring was continued, at rt, for 4h. A solution of NaOH 1N was added and the MeOH was evaporated. The mixture was extracted with EtOAc twice and the organic layer was washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The isolated amines were either used without further purification or purified by flash chromatography (EtOAc/heptane: 2/8), depending on the purity.

Typical procedure (K) for an anhydride coupling

To a sol. of the bicyclononene (0.05 mmol) in CH_2Cl_2 (0.4 mL) was added DIPEA (0.1 mmol) followed by the anhydride (0.06 mmol) in CH_2Cl_2 (0.4 mL) at 0°C. After stirring for 3h at rt, the solvent was evaporated under reduced pressure.

Typical procedure (L) for protecting group (BOC and TBDMS) cleavage

To a sol. of the bicyclononene (0.05 mmol) in CH_2Cl_2 (0.5 mL), cooled to 0°C, was added 4M HCl/dioxane(0.5 mL) The ice bath was removed and the solution was stirred for 1h30 to 3h, depending on the compound. The solvents were evaporated under reduced pressure without heating.

Typical procedure (M) for the saponification of esters

A mixture of the ester (1 eq.) and LiOH (2 eq.) in THF was stirred at rt for 2 h. The solvents were removed under reduced pressure and the residue was extracted on isolute sorbent (0.25 g pre-washed with 0.300 mL aq. 1M HCl, elution with 2

mL CH_2Cl_2). The solvent was removed under reduced pressure and the residue was used without further purification.

Preparation of amines

(2-Chlorobenzyl)cyclopropylamine

Synthesized according to typical procedures B and D from 2-chlorobenzoyl chloride and cyclopropylamine.

Benzylcyclopropylamine

See Loeppky, R. N.; *et al.*, *J. Org. Chem.*, **2000**, *65*, 96.

(2-Chlorobenzyl)ethylamine

See Ishihara, Y; *et al.*; *Chem. Pharm. Bull.*, **1991**, *39*, 3225.

Cyclopropyl-(3-trifluoromethylbenzyl)amine

See Brabander, H. J.; *et al.*; *J. Org. Chem.*, **1967**, *32*, 4053.

Cyclopropylphenethylamine

See Smith, P. W.; *et al.*; *J. Med. Chem.*, **1998**, *41*, 787.

Methyl(3-phenoxypropyl)amine

Synthesized according to typical procedures C and D from 3-phenoxypropionic acid and methylamine.

(2-*p*-Tolyloxyethyl)methylamine

Synthesized according to typical procedures C and D from 2-*p*-tolyloxyacetic acid and methylamine.

[2-(3-Chlorophenyl)ethyl]amine

Synthesized according to typical procedures C and D from 3-chlorophenylacetic acid and methylamine.

[2-(2-Methoxyphenyl)ethyl]amine

Synthesized according to typical procedures C and D from 2-methoxyphenylacetic acid and methylamine.

(2-Allylbenzyl)cyclopropylamine

BuLi (1.55 M in hexane, 14.7 mL, 22.7 mmol) was added to a sol. of 1-bromo-2-(dimethoxymethyl)benzene (5.00 g, 21.6 mmol) in Et_2O (50 mL). The mixture was stirred for 30 min at –78 °C and $MgBr_2 \cdot Et_2O$ (5.87 g, 22.7 mmol) was added. The mixture was allowed to warm up to 0 °C over 15 min and CuI (420 mg, 2.16 mmol) was added. The mixture was stirred at 0 °C for 5 min and allyl bromide (1.92 mL, 22.7 mmol) was added. The mixture was stirred overnight while warming up to rt. Aq. 1M HCl (1 mL) was added and the mixture was diluted with Et_2O, and washed with aq. 1M HCl (1x). The org. Extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was dissolved in acetone (20 mL) and water (10 mL), and TosOH (cat. amount) was added. The mixture was stirred for 5 h at rt, and the solvents were partially removed under reduced pressure. The residue was diluted with Et_2O, and washed with aq. 1M HCl (1x), and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (Et_2O/petroleum ether 1:49 → 24:1)

yielded 2-allylbenzaldehyde (1.06 g, 34%). This compound was transformed into the title compound following typical procedure J with cyclopropylamine.

Cyclopropyl(2-fluorobenzyl)amine

Synthesized according to typical procedure J from 2-fluorobenzaldehyde and cyclopropylamine.

Cyclopropyl-(2-methylbenzyl)amine

Synthesized according to typical procedure J from 2-methylbenzaldehyde and cyclopropylamine.

Cyclopropyl-[2-(4-methoxyphenoxy)ethyl]amine

Synthesized according to typical procedures C and D from (4-methoxyphenoxy)-acetic acid and cyclopropylamine.

Cyclopropyl-[2-(3-methoxyphenoxy)ethyl]amine

Synthesized according to typical procedures C and D from (3-methoxyphenoxy)-acetic acid and cyclopropylamine.

Cyclopropyl-(2-*o*-tolyloxyethyl)amine

Synthesized according to typical procedures C and D from *o*-tolyloxyacetic acid and cyclopropylamine.

Cyclopropyl-[2-(3,4-dimethylphenoxy)ethyl]amine

Synthesized according to typical procedures C and D from (3,4-dimethyl-phenoxy)acetic acid and cyclopropylamine.

[2-(2-Chlorophenyl)ethyl]cyclopropylamine

Synthesized according to typical procedures C and D from (2-chlorophenyl)-acetic acid and cyclopropylamine.

Cyclopropyl-[2-(2,3-difluorophenyl)ethyl]amine

Synthesized according to typical procedures C and D from (2,3-difluorophenyl)-acetic acid and cyclopropylamine.

Cyclopropyl-[2-(4-fluorophenyl)ethyl]amine

Synthesized according to typical procedures C and D from (4-fluorophenyl)acetic acid and cyclopropylamine.

Cyclopropyl-(2-*o*-tolylethyl)amine

Synthesized according to typical procedures C and D from *o*-tolylacetic acid and cyclopropylamine.

Cyclopropyl-(2-*p*-tolylethyl)amine

Synthesized according to typical procedures C and D from *p*-tolylacetic acid and cyclopropylamine.

Cyclopropyl-(3,5-dimethoxybenzyl)amine

Synthesized according to typical procedure J from 2,5-dimethoxybenzaldehyde and cyclopropylamine.

(2-Chlorobenzyl)methylamine

See Kihara, M; et al.; *Heterocycles*, **1989**, *29*, 957.

(2-Chlorobenzyl)isopropylamine

Synthesized according to typical procedure J from 2-chlorobenzaldehyde and isopropylamine.

Cyclopropyl-(2-fluoro-5-methoxybenzyl)amine

Synthesized according to typical procedure J from 2-fluoro-5-methoxybenzaldehyde and cyclopropylamine.

Cyclopropyl-(3-methoxybenzyl)amine

Synthesized according to typical procedure J from 3-methoxybenzaldehyde and cyclopropylamine.

Cyclopropyl-(3,4-dimethoxybenzyl)amine

Synthesized according to typical procedure J from 3,4-dimethoxybenzaldehyde and cyclopropylamine.

(2-Chloro-3-trifluoromethylbenzyl)cyclopropylamine

Synthesized according to typical procedure J from 2-chloro-3-trifluoromethylbenzaldehyde and cyclopropylamine.

(6-Chlorobenzo[1,3]dioxol-5-ylmethyl)cyclopropylamine

Synthesized according to typical procedure J from 6-chlorobenzo[1,3]dioxole-5-carbaldehyde and cyclopropylamine.

Cyclopropyl-(5-fluoro-2-methoxybenzyl)amine

Synthesized according to typical procedure J from 5-fluoro-2-methoxybenzaldehyde and cyclopropylamine.

(2-Chloro-6-fluorobenzyl)cyclopropylamine

Synthesized according to typical procedure J from 2-chloro-6-fluorobenzaldehyde and cyclopropylamine.

(2-Bromobenzyl)cyclopropylamine

Synthesized according to typical procedure J from 2-bromobenzaldehyde and cyclopropylamine.

Cyclopropyl-(2,6-difluorobenzyl)amine

Synthesized according to typical procedure J from 2,6-difluorobenzaldehyde and cyclopropylamine.

Cyclopropyl-(2,3-dimethylbenzyl)amine

Synthesized according to typical procedure J from 2,3-dimethylbenzaldehyde and cyclopropylamine.

Cyclopropyl-(3-fluoro-2-methylbenzyl)amine

Synthesized according to typical procedure J from 3-fluoro-2-methylbenzaldehyde and cyclopropylamine.

Cyclopropyl-(3,5-difluorobenzyl)amine

Synthesized according to typical procedure J from 3,5-difluorobenzaldehyde and cyclopropylamine.

(2-Chloro-3,6-difluorobenzyl)cyclopropylamine

Synthesized according to typical procedure J from 2-chloro-3,6-difluorobenzaldehyde and cyclopropylamine.

(2,3-Dichlorobenzyl)cyclopropylamine

Synthesized according to typical procedure J from 2,3-dichlorobenzaldehyde and cyclopropylamine.

Cyclopropyl-(3-trifluoromethoxybenzyl)amine

Synthesized according to typical procedure J from 3-trifluoromethoxy-benzaldehyde and cyclopropylamine.

Cyclopropyl-(3-methylbenzyl)amine

Synthesized according to typical procedure J from 3-methylbenzaldehyde and cyclopropylamine.

Cyclopropyl-(2,3-difluorobenzyl)amine

Synthesized according to typical procedure J from 2,3-difluorobenzaldehyde and cyclopropylamine.

(3-Chlorobenzyl)cyclopropylamine

Synthesized according to typical procedure J from 3-chlorobenzaldehyde and cyclopropylamine.

Cyclopropyl-(4-fluorobenzyl)amine

Synthesized according to typical procedure J from 4-fluorobenzaldehyde and cyclopropylamine.

Preparation of other reagents

4-Carbamoylbutyric acid

See Melnyk, O., et al.; *J. Org. Chem.*, **2001**, *66*, 4153.

***meso*-3,4-Dihydroxytartaric acid anhydride**

A mixture of *meso*-3,4-Diydroxytartaric acid (1.00 g, 6.67 mmol) and trifluoroacetic acid anhydride (5 mL) was stirred for 2 h at rt. The solvents were removed under reduced pressure and the residue was used as crude product without further purification.

Succinamic acid

See Bellier, B., et al.; *J. Med. Chem.*, **2000**, *43*, 3614.

Specific examples

Preparation of example 64 is described in detail. The other examples depicted in Table 1 can be prepared according to the same procedures and according to descriptions given in WO 03/093267 A1 (Actelion Pharmaceuticals Ltd.) or by analogous methods.

Example 64

(*rac.*)-5-((*1R, *5S**)-7-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-6-{[2-(2,3-difluorophenyl)ethyl]cyclopropylcarbamoyl}-3,9-diazabicyclo[3.3.1]non-6-en-3-yl)-5-oxopentanoic acid formate salt**

Synthesized according to typical procedures K and E from bicyclononene **AL31** and glutaric anhydride. LC-MS: $R_t = 0.90$; ES+: 768.35.

Table 1 lists preferred compounds of the invention and their *in vitro* activity against plasmepsin II (determined as described above).

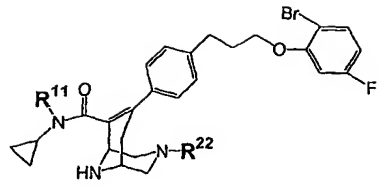
Activities are classified as follows:

Activity class A: IC_{50} (Plasmepsin II) < 10 nM

Activity class B: 10 nM < IC_{50} (Plasmepsin II) < 100 nM

Activity class C: 100 nM < IC_{50} (Plasmepsin II) < 10 μM

Table 1:



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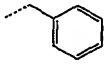
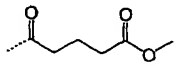
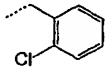
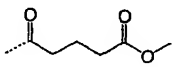
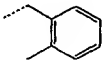
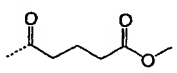
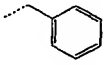
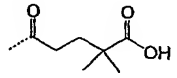
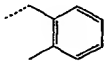
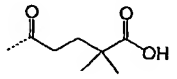
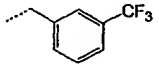
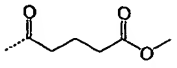
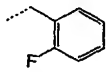
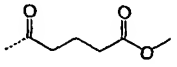
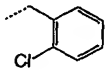
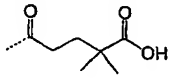
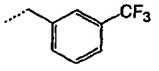
1			A
2			A
3			A
4			A
5			A
6			A
7			A
8			A
9			A

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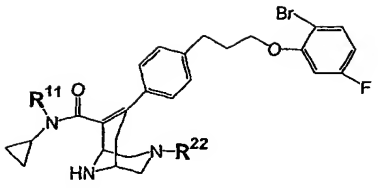

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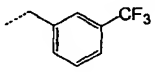
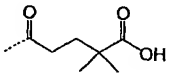
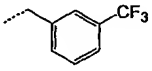
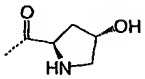
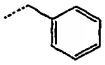
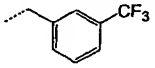
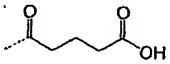
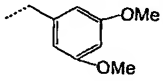
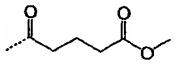
10			A
11			A
12			A
13			B
14			B

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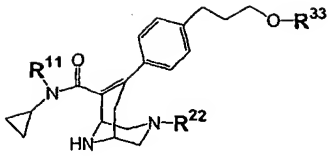


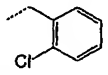
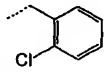
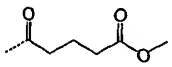
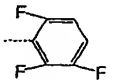
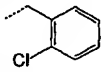
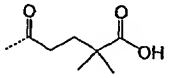
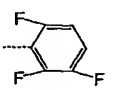
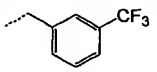
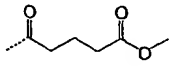
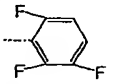
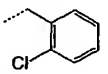
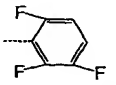
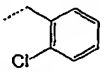
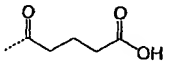
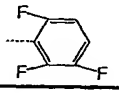
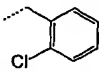
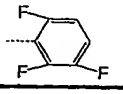
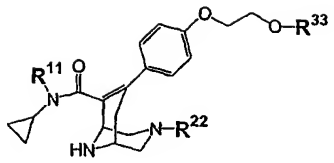
Ex. No.	R^{11}	R^{22}	R^{33}	Activity Class
15				A
16				B
17				C
18				C
19				C
20				C
21				C

Table 1 continued:



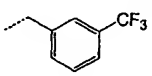
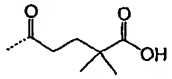
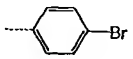
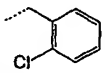
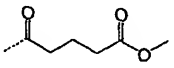
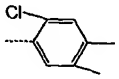
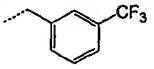
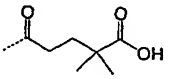
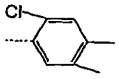
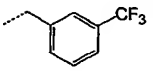
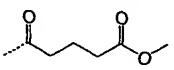
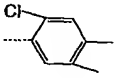
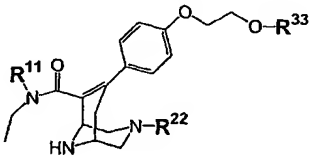
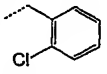
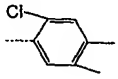
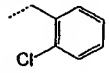
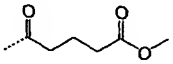
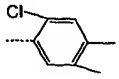
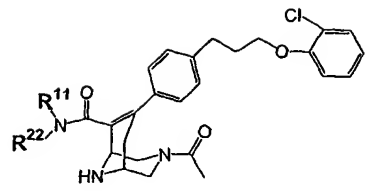
Ex. No.	R^{11}	R^{22}	R^{33}	Activity Class
22				C
23				C
24				C
25				C
				
26				C
27				C

Table 1. continued:



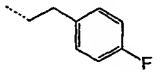
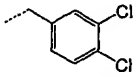
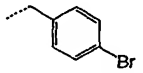
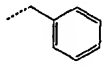
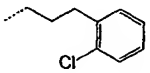
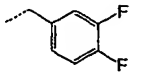
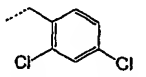
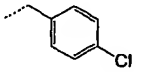
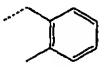
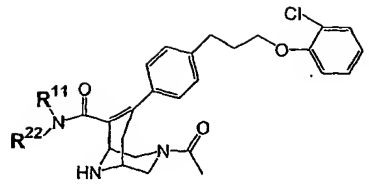
Ex. No.	R^{11}	R^{22}	Activity Class
28		----CH_3	A
29		----CH_3	A
30		----CH_3	A
31			A
32		----CH_3	A
33		----CH_3	A
34		----CH_3	A
35		----CH_3	A
36		----CH_3	A

Table 1 continued:



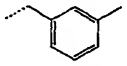
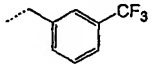
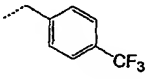
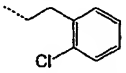
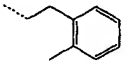
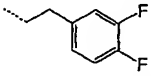
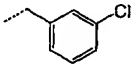
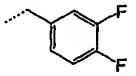
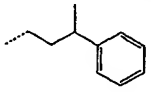
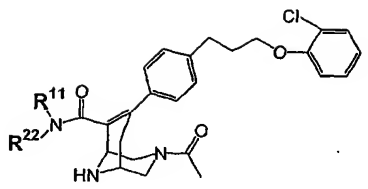
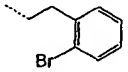
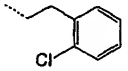
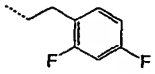
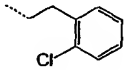
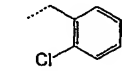
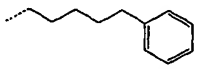
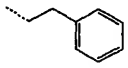
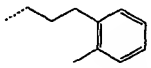
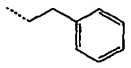
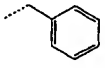
Ex. No.	R^{11}	R^{22}	Activity Class
37		····CH_3	A
38		····CH_3	A
39		····CH_3	A
40		····CH_3	A
41		····CH_3	A
42		····CH_3	A
43		····CH_3	A
44		····CH_3	A
45		····CH_3	A

Table 1 continued:



Ex. No.	R^{11}	R^{22}	Activity Class
46			B
47			B
48			B
49			B
50			C
51			C
52			C
53			B
54			C

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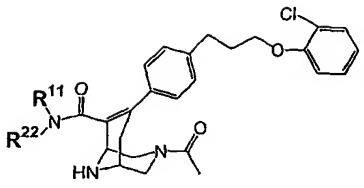
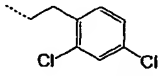
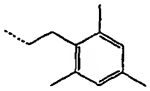


Ex. No.	R^{11}	R^{22}	Activity Class
55			C
56			C

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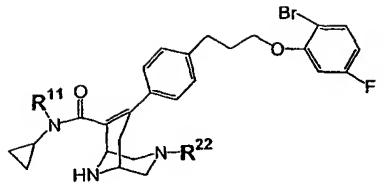


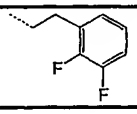
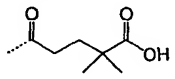
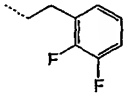
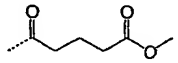
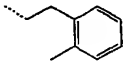
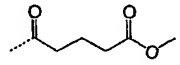
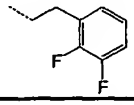
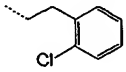
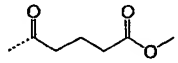
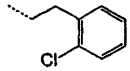
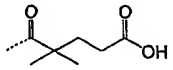
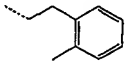
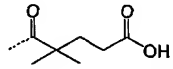
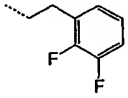
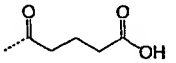
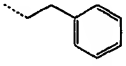
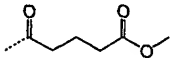
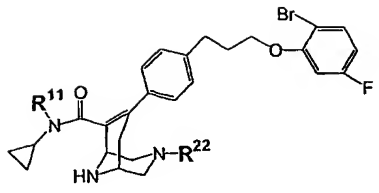
Ex. No.	R^{11}	R^{22}	Activity Class
57			A
58			A
59			A
60			A
61			A
62			A
63			A
64			A
65			A

Table 1 continued:



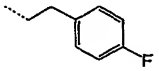
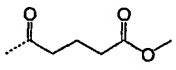
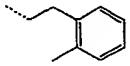
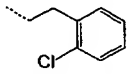
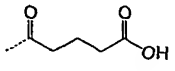
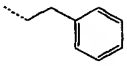
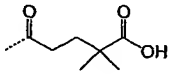
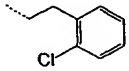
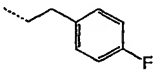
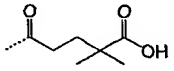
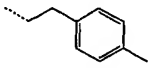
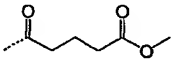
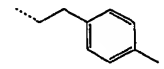
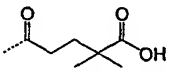
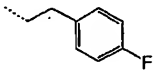
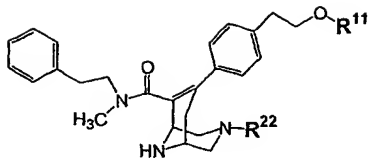
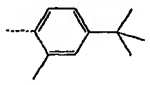
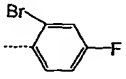
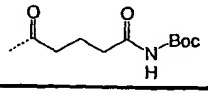
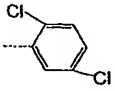
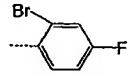
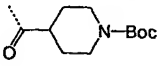
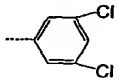
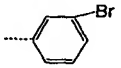
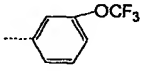
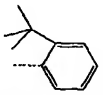
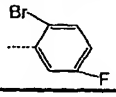
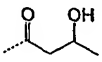
Ex. No.	R^{11}	R^{22}	Activity Class
66			B
67			B
68			B
69			B
70			B
71			B
72			B
73			B
74			B

Table 1 continued:



Ex. No.	R^{11}	R^{22}	Activity Class
75			B
76			B
77			B
78			B
79			B
80			B
81			B
82			B
83			B

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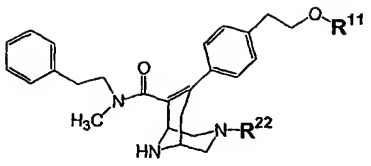
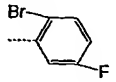
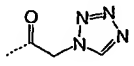
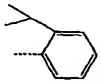
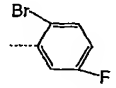
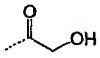
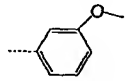
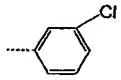
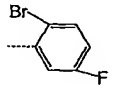
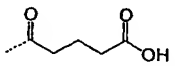
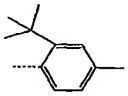


Ex. No.	R^{11}	R^{22}	Activity Class
84			B
85			B
86			B
87			B
88			C
89			C
90			C

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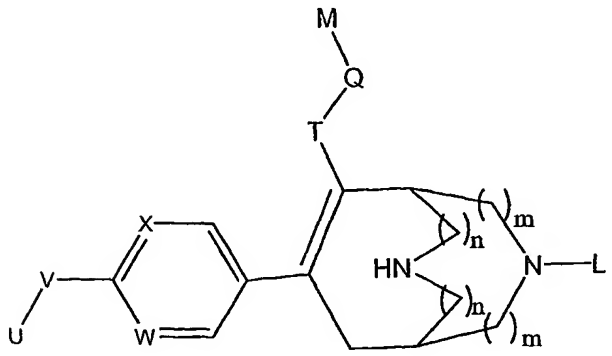
Claims

1. Pharmaceutical compositions for treating diseases demanding the inhibition of parasite aspartic proteases containing one or more compound(s) of the general formula **I**,



General formula **I**

wherein

X and W represent a nitrogen atom or a -CH- group and may be the same or different;

V represents $-(CH_2)_r-$; $-A-(CH_2)_s-$; $-CH_2-A-(CH_2)_t-$; $-(CH_2)_s-A-$; $-(CH_2)_2-A-(CH_2)_u-$; $-A-(CH_2)_v-B-$; $-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-B-$; $-CH_2-CH_2-CH_2-A-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-CH_2-$; $-CH_2-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-CH_2-B-$; or $-CH_2-CH_2-A-CH_2-CH_2-B-$;

A and B independently represent -O-; -S-; -SO-; $-SO_2-$;

U represents aryl; heteroaryl;

T represents $-CONR^1-$; $-(CH_2)_pOCO-$; $-(CH_2)_pN(R^1)CO-$; $-(CH_2)_pN(R^1)SO_2-$; or -COO-;

Q represents lower alkylene; lower alkenylene;

M represents hydrogen; cycloalkyl; aryl; heterocyclyl; heteroaryl;

L represents $-R^3$; $-COR^3$; $-COOR^3$; $-CONR^2R^3$; $-SO_2R^3$; $-SO_2NR^2R^3$; $-COCH(Aryl)_2$;

R^1 represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

R^2 and $R^{2'}$ independently represent hydrogen; lower alkyl; lower alkenyl; cycloalkyl; cycloalkyl - lower alkyl;

R^3 represents hydrogen; lower alkyl; lower alkenyl; cycloalkyl; aryl; heteroaryl; heterocyclyl; cycloalkyl - lower alkyl; aryl - lower alkyl; heteroaryl - lower alkyl; heterocyclyl - lower alkyl; aryloxy - lower alkyl; heteroaryloxy - lower alkyl, whereby these groups may be unsubstituted or mono-, di- or trisubstituted with hydroxy, $-OCOR^2$, $-COOR^2$, lower alkoxy, cyano, $-CONR^2R^{2'}$, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), $-NH(NH)NH_2$, $-NR^4R^{4'}$ or lower alkyl, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

R^4 and $R^{4'}$ independently represents hydrogen; lower alkyl; cycloalkyl; cycloalkyl - lower alkyl; hydroxy - lower alkyl; $-COOR^2$; $-CONH_2$;

m and n represent the integer 0 or 1, with the proviso that in case m represents the integer 1 n is the integer 0, and in case n represents the integer 1 m is the integer 0;

p is the integer 1, 2, 3 or 4;
r is the integer 3, 4, 5, or 6;

s is the integer 2, 3, 4, or 5;

t is the integer 1, 2, 3, or 4;

u is the integer 1, 2, or 3;

v is the integer 2, 3, or 4;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms and suitable carrier materials.

2. Pharmaceutical compositions according to claim 1 for treatment of disorders associated with the role of plasmepsin II and which require inhibition of plasmepsin II for treatment.

3. Pharmaceutical compositions according to claim 1 for treatment or prevention of malaria.

4. Pharmaceutical compositions according to claim 1 for treatment or prevention of diseases caused by protozoal infection.

5. Pharmaceutical compositions according to claim 1 which contain aside of one or more compounds of the general formula I a known plasmepsin II inhibitor, a known antimalarial or a known HIV protease inhibitor.

6. Use of pharmaceutical compositions according to any one of claims 1 to 5 for treatment or prevention of diseases demanding the inhibition of parasitic aspartic proteases.

7. Use of pharmaceutical compositions according to any one of claims 1 to 5 for treatment or prevention of malaria.

8. Use of pharmaceutical compositions according to any one of claims 1 to 5 for treatment or prevention of protozoal infections.

9. Use of pharmaceutical compositions according to any one of claims 1 to 5 for treatment or prevention of diseases demanding the inhibition of parasitic aspartic proteases in combination with a known plasmepsin II inhibitor, a known antimalarial or a known HIV protease inhibitor or another known anti-HIV treatment.

10. Use of a compound of formula I in claim 1 for the preparation of a medicament for the treatment or prevention of diseases demanding the inhibition of parasitic aspartic proteases.

11. Use according to claim 10 wherein said disease is malaria.

12. Use according to claim 10 wherein said disease is protozoal infection.

13. Use of a compound of formula I in claim 1 for the preparation of a medicament for the treatment or prevention of diseases demanding the inhibition of parasitic aspartic proteases in combination with a known plasmepsin II inhibitor, a known antimalarial or a known HIV protease inhibitor or another known anti-HIV treatment.

14. A method of treating a patient suffering from a disease requiring the inhibition of parasitic aspartic proteases by administering a pharmaceutical composition according to any one of claims 1 to 5.

15. A method according to claim 14 by administering a dose of the parasitic aspartic protease inhibitor of the general formula I between 1 mg and 1000 mg per day.

16. A method according to claim 14 by administering a dose of the parasitic aspartic protease inhibitor of the general formula I between 1 mg and 500 mg per day.

17. A method according to claim 14 by administering a dose of the parasitic aspartic protease inhibitor of the general formula I between 5 mg and 200 mg per day.

18. A process for the preparation of a pharmaceutical composition according to any one of the claims 1 to 5, characterized by mixing one or more active ingredients according to claim 1 with inert excipients in a manner known per se.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/005065

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4995 A61P33/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03/093267 A (REMEN LUBOS ; WELLER THOMAS (CH); BUR DANIEL (CH); FISCHLI WALTER (CH)) 13 November 2003 (2003-11-13) cited in the application Abstract; page 1, lines 9-13; claims (PX-document for inventive step).	1-18
A	WO 99/12532 A (HOFFMANN LA ROCHE ; BUR; FISCHLI; MATILE; RIDLEY; WOSTL) 18 March 1999 (1999-03-18) cited in the application Page 1, lines 7-10; claims.	1-18
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 September 2004	06/10/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Weisbrod, T

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/005065

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/14331 A (ELLMAN JONATHAN A ; GOLDBERG DANIEL (US); KIM JIN MI (US); UNIV CALIFO) 1 March 2001 (2001-03-01) cited in the application Abstract; page 2, lines 9-14; claims; examples.	1-18
A	BURSAVICH, M. G.; RICH, D. H.: "Designing Non-Peptide Peptidomimetics in the 21st Century: Inhibitors Targeting Conformational Ensembles" J. MED. CHEM., vol. 45, no. 3, 2002, pages 541-558, XP002297081 Pages 548-551; compounds 21 to 25.	1-18
P,A	BOSS, C. ET AL.: "Inhibitors of the Plasmodium Falciparum Parasite Aspartic Protease Plasmepsin II As Potential Antimalarial Agents" CURR. MED. CHEM., vol. 10, no. 11, 2003, pages 883-907, XP009036752 cited in the application the whole document	1-18
A	CHEN X ET AL: "Potent piperazine hydroxyethylamine HIV protease inhibitors containing novel P3 ligands" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 24, 15 December 1998 (1998-12-15), pages 3531-3536, XP004150362 ISSN: 0960-894X Compounds I.	1-18
A	EL-ABBADY S A ET AL: "ENHANCED REACTIVITY OF PYRIDIN-3-OL TOWARDS 4-PHENYL-1,2,4-TRIAZOLINE 3,5-DIONE: FMO TREATMENT OF THE CYCLOADDITION PROCESS BY ASED-MO CALCULATIONS METHOD" ZAGAZIG JOURNAL OF PHARMACEUTICAL SCIENCES, FACULTY OF PHARMACY ZAGAZIG UNIVERSITY, CAIRO, EG, vol. 5, no. 1, June 1996 (1996-06), pages 68-74, XP001154254 ISSN: 1110-5089 Page 70, compound 5.	1-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/005065

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 6-9 and 14-17 are directed to methods of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds/compositions.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/005065

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03093267 A	13-11-2003	WO 03093267 A1	13-11-2003
WO 9912532 A	18-03-1999	AU 9740998 A	29-03-1999
		WO 9912532 A2	18-03-1999
WO 0114331 A	01-03-2001	AU 6936500 A	19-03-2001
		WO 0114331 A2	01-03-2001